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THE ADRENAL GLANDS*

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CLEVELAND

Since 1915, Dr. J. M. Rogoff has collaborated with me in all the work on the adrenal glands. It has been a joint research, and even when I speak in the first person singular I include him. Further, the investigation, although extending over a long time, was planned as one continuous piece of work on the two glands constituting the adrenal bodies. As it was planned, so it was carried out, with few modifications. The work on the interrenal gland overlapped that on the chromaffin tissue, but when the latter had been proved to possess only slight physiologic significance, or, at any rate, not to be concerned essentially in the preservation of health and life, we decided to spend no further time on the medulla but to concentrate all our efforts on the cortex. Many interesting facts, however, were discovered in regard to the liberation of epinephrine from the medulla, and previously known facts were confirmed and amplified, some of which are herein mentioned.

In this paper, no attempt is made to cover the whole field of the physiology and pathology of the adrenal glands. This is much too extensive even to be sketched in the time at our disposal. The literature is vast and continually growing. Unfortunately, much of the work is, for various reasons, so poor that it is kept alive only through the conscientious efforts of authors to notice everything that has been written. It would be a distinct advantage if many papers, not necessarily the earlier ones alone, could be forgotten. To describe everything in detail, to analyze and to controvert what is wrong would require the writing of a shelf of books. A complete account even of what has been already ascertained, or of what is more or less plausibly conjectured, would fill a good sized volume. All that can be done here is to select what seem the most important and best established results, particularly the more recent ones, to connect them, as far as possible, with each other and,

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* From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

perhaps, in certain instances to relate them to properties and functions of other tissues, as a contribution toward a future theory of the functions of the glands.

The active substance of the medulla having been discovered and isolated at a time when hardly anything was known about the cortex, it is unfortunate, though natural, that adrenalin or epinephrine should have at once assumed the place of the hormone of the adrenal gland. It has been so designated almost everywhere, not only in textbooks of physiology but, with hardly an exception, in textbooks of medicine and in clinical writings generally; this error has persisted to the present hour. As the adrenal gland is unquestionably important, being, in fact, indispensable to life, it seemed necessary to invest the only known active principle of the gland with important physiologic functions, particularly as the pharmacologic actions of the substance (usually in much larger concentration than can ever exist in the arterial blood) are manifold and most striking. Everywhere, then, the importance of epinephrine was emphasized. It sustained the blood pressure by its vasoconstrictor action. It titillated the heart when it tended to lag and grow weary and kept it to its never ending task. It influenced the tone of all muscular structures innervated by the sympathetic nervous system. It caused the pupils to dilate, the eyeballs to appear more prominent and menacing, and the hair on the tail and back to be erected when animals were stirred by rage or anger. It participated in the physical accompaniments of the emotions aroused by combat. It even caused the blood to clot faster if the combatant was wounded. It was the only one of the internal secretions which seemed to be completely anti-pacifist. No wonder it became popular. No wonder many came to agree with Cybulski, who wrote at the time when indications of what is now called epinephrine or adrenalin were found by him in the adrenal veins: "The nervous system is now dethroned." This absurd dictum and all that it implies became embedded in the physiology of the clinician. If standard textbooks of medicine are consulted today as to the pathology of Addison's disease they still announce that it is the loss of epinephrine that causes the chief symptoms, including, of course, the fall of blood pressure. Usually the cortex is never mentioned. The consequence of all this is that the average reader rises from his study of the works usually available to him deeply impressed with the varied and potent actions of the epinephrine liberated by the medulla, but scarcely conscious that the cortex is anything else than what used to be called a vestigial remnant without physiologic significance. It is probably safe to say that nine tenths of the medical profession are completely ignorant of the physiology of the adrenal bodies, or, what is far worse, have minds so well stored with erroneous information that truth finds them hard to penetrate. Many generally

well informed students, if asked what would happen were the adrenal medulla to cease delivering epinephrine to the blood, would probably answer that a severe fall in the blood pressure would occur, while the emotions of the sufferer, in the presence of the physiologic catastrophe, would have to remain unexpressed.

I am not sanguine enough to suppose that such errors can be eradicated easily; nor is it my business to carry on a crusade against them. It is not important that they should linger on for a while. In time all these matters will be put right. On the present occasion, however, the opportunity offered of restating the salient facts in regard to the supposed functions of the medulla need not be neglected. The chief part of the paper will deal with the newer work on the cortex.

To forestall a possible criticism, or at least to prevent ambiguity, it may be stated at the beginning that I generally use the term adrenal rather than suprarenal even in the cases in which the latter is anatomically correct, as in man. In one of the common laboratory animals, the guinea-pig, the large adrenal bodies lie cephalad to the kidneys rather than beside them, and might be denominated suprarenal rather than adrenal glands, if the mere anatomic relations were to govern the terminology. These relations, however, whatever their occasional interest in surgery and pathology, have no functional significance. It seems better, therefore, to employ one name for the same tissues irrespective of their anatomic relations to the kidneys.

The important experimental data have been obtained on the adrenal glands of animals. If the same word is to be employed to characterize one and the same structure, the use of the term adrenal should be extended to take in the human gland. The opposite rule of using the word "suprarenal" indiscriminately in dogs, cats, rabbits, rats, guinea-pigs, etc., as well as in man, is insisted on by some editors for reasons difficult to fathom. It certainly seems clumsy to speak of the suprarenal glands of a rat or a cat—quite as clumsy as it would seem to speak of the adrenal glands of a man. No harm is done in either case if the self-respect of the necessary, harmless contributor is not outraged in the process of securing uniformity.

More than seventy years have elapsed since Addison published his observations on the "constitutional and local effects of disease of the suprarenal capsules." It shows a penetrating judgment that from a clinical and postmortem study of certain cases of the syndrome now called Addison's disease he should have unveiled a relationship, since abundantly confirmed, between the syndrome and a destructive lesion, especially tuberculous, in the suprarenal glands. His observations, however, are not always easy to understand. For instance, in four of the eleven cases described, the lesion was unilateral. Now destruction of one adrenal gland in animals is harmless. Yet, apparently, the

clinical symptoms were present in these four cases as well as in the remaining seven in which the lesions were bilateral. It may be that Addison was in error in regarding the lesion as unilateral in the four cases mentioned. Microscopic examination might have revealed destructive changes in both capsules. Certain more recent writers, however, have described cases of Addison's disease associated with a unilateral lesion.

At that time it was not recognized that the adrenal body in mammals consists of two glands, the cortex or interrenal gland and the medulla or chromaffin tissue. Even to this day it is not uncommon for authors to refer to the adrenal gland as if it were homogeneous in structure and in function. No apology, therefore, need be made for stating at this point that the cortex and medulla are considered herein as two distinct organs. The mere fact that the medulla is embedded in the cortex changes nothing except that it entails some modification of the blood supply. Until this was made clear, it was impossible to advance far in the study of the adrenal glands, just as it was impossible to advance far in the study of the thyroid gland until the parathyroid glands were discovered and shown to be separate organs with completely different functions.

Several years ago, in discussing the subject of adrenalectomy and the relation of the adrenals to metabolism, I stated that "if the cortex is the important part of the adrenal it would seem logical in considering the special relations of the gland to metabolism to take the cortex first. It happens, however, that by far the greatest amount of work has been done upon the medulla, the reason being that it forms and gives off a well characterized substance, epinephrine, which in sufficient doses causes many striking reactions, including definite metabolic effects." For that reason the medulla was taken up first and at considerable length, while the more important cortex was relegated to the end of the paper and treated briefly. In the interval which has elapsed, much progress has been made in knowledge of the cortex, largely through the researches carried out in this laboratory by Dr. J. M. Rogoff and myself. Dr. de Necker, Dr. R. Dominguez and Dr. Ecker have also collaborated with Dr. Rogoff in investigating certain points. It will, therefore, be best to reverse the order in the present paper and to deal first with the really important gland of the adrenal body, the interrenal gland or cortex.

THE INTERRENAL GLAND OR CORTEX

It is not possible to extirpate the cortex except by removing the entire adrenal body. Proof will be given that the medulla or chromaffin tissue can be taken away without affecting the health or life of the

animal. The consequences which follow total adrenalectomy are quite different and may, therefore, be attributed to loss of the function of the cortex.

A large proportion of white rats survive indefinitely the loss of both adrenal glands. The same is true of wild (sewer) rats, as shown by Boinet more than thirty years ago. Rogoff and de Necker found that in large batches of good stock, fully 50 per cent of white rats, and in some batches still more, may survive, apparently for an indefinite time. Of adult rabbits, not less than 25 per cent—under the best conditions, considerably more—recover completely after excision of the two adrenal glands and live indefinitely. A large additional number survive for several weeks. The fact that many rats and rabbits survive the loss of the adrenal glands has generally been attributed to the presence of accessory adrenal glands composed of tissue like the cortex, so that in these animals the operation sometimes remains incomplete. While this explanation may be accepted for some of the animals it cannot be considered as proved for all. Nor has the amount of tissue necessary to keep an animal alive been ascertained so exactly that an accessory, when found can be confidently said to suffice.

The dog is an animal in which, according to macroscopic observations, accessory adrenal glands are exceedingly rare. One was encountered in 150 dogs, and this was seen at the time of operation and removed. Dogs always die after total adrenalectomy. If the technic is adequate, they do not die from the operation as such but from the syndrome which is called adrenal insufficiency, and which develops after a longer or shorter period of good health. We have accumulated no less than 200 of these "control" dogs in which the adrenal glands were removed one at a time, with an interval of from one to many weeks between the two operations. The results on the control animals, not subjected to any treatment, form the indispensable standard of comparison when a given method of treatment, or the effect of certain physiologic conditions on the consequences of total adrenalectomy is being tested. In certain cases, the control series has been swelled by the addition of animals in which a given treatment has had a clearly negative result. It is not necessary to reproduce tables in which the results on control dogs have been embodied. They can be found in several of our published papers.

It may be said that most dogs operated on according to our technic survive the removal of the second adrenal gland for at least a week. Many live for ten or twelve days, a few for fourteen or fifteen days, and in rare instances the dogs live for fewer than five or six days. One dog of 150 was seen to survive sixteen and a quarter days. None of the dogs die in as short a time as twenty-four hours, and we are inclined to believe that when an animal survives for only two or three days, it does not die of adrenal insufficiency alone. We do not think

averages of such series of much use, but the average for our dogs is about eight days; for the last series it was nine and a half days.

Cats survive longer than dogs. The average in our laboratory for nearly fifty cats was eleven days. The majority lived for from one to two weeks. A few survived three weeks, and one about thirty days. One cat survived for thirty-one and a half days, and one, a castrated male, which was not included among the controls, more than thirty-five days. In accumulating control dogs and cats, only male or nonpregnant female animals are chosen. No female ascertained to be in heat at the time that the second operation would be performed is taken. The reasons for these restrictions will appear later.

It scarcely need be said that in all animals used in either series, for control or treatment, most careful search was made both at operation and post mortem for accessory adrenal glands. Accessory adrenal glands were seen in two cats and removed at operation. In one cat, two accessories were observed at the first operation and purposely left behind; a third was found post mortem. The animal lived for fourteen days and was not included among the controls.

Guinea-pigs in our laboratory have been found to survive much longer than any mentioned in the literature, although not as long as cats or dogs. Many of them live about a week—a few longer.

We have dwelt on this matter of the control series because in judging the effect of a given treatment or a given physiologic condition on survival, everything depends on a comparison with a sufficiently large series of controls. In our opinion, these should be operated on by the same observers who operate on the animals in the treatment series and under the same conditions. Only when both series are accumulated in the same laboratory can a real check be made.

Our results differ greatly from most of those in the literature. Beginning with Brown-Séquard, and in the case of other animals than dogs, statements as to the time of survival and the behavior after adrenalectomy are seen to be impossible of acceptance, because the animals obviously died as a result of poor surgical technic rather than adrenal insufficiency. The symptoms of adrenal insufficiency could rarely, if ever, develop clearly and uncomplicated by other symptoms not connected directly with elimination of the cortical functions. Whatever study might be given to the picture, it was bound to be unsatisfactory because of the clouding effects of the operation. Further, the study was necessarily too transitory because the period of survival was so short.

Perhaps the best illustration which can be given of the absolute necessity of good technic in drawing conclusions as to the effects of loss of the adrenal glands is the work of Brown-Séquard. Not long after the publication of Addison's paper, he extirpated the glands in

different species of animals, and is credited with being the first to prove that they are indispensable to life. This conclusion is certainly true in dogs, cats and guinea-pigs, in most rabbits and in some rats; Brown-Séquard, however, did not prove it. All the animals which he operated on, including rats, rabbits, guinea-pigs, cats and dogs died in from nine to thirty-seven hours. Even when he removed only one gland from rabbits, guinea-pigs, cats and dogs, none survived longer than from twenty-three to twenty-four hours. It is now well known that removal of one suprarenal gland, far from being fatal, does not affect the health or shorten the life of any animal operated on under proper conditions. It was pointed out at the time by Phillipeau that there were other causes than the loss of an indispensable function which might account for the fatal consequences of Brown-Séquard's operations, for example, hemorrhage and sepsis, both extremely common. Cooling, perhaps undue prolongation of operations, inadequate care before and after operation and excessive trauma in a field peculiarly susceptible to trauma almost certainly contributed to the bad results. In any case, what has been said shows clearly that Brown-Séquard was not in a position to draw any conclusion from his results.

It has not been sufficiently recognized, perhaps, that the surgical difficulties in adrenalectomy are, except in rats, greater than in operations on most of the other endocrine glands. Removal of the thyroid gland is simple; so is removal of the parathyroid glands as soon as they are recognized. Gonadectomy is easy in the male and not difficult in the female in the laboratory animals. Complete pancreatectomy is, of course, an operation requiring skill. Operations on the pituitary gland are difficult on account of the formidable approach and for other reasons. In the case of the adrenal glands, the right gland in the guinea-pig lies close against the vena cava and under the liver; the vessels are delicate and liable to injury. In the rabbit this is true also, but not to the same degree. In the dog, the operative field lies deep and the right gland is close to the vena cava. Next to the guinea-pig, then, among the common laboratory animals, the dog is the animal whose right adrenal gland is most difficult to excise. In the cat, the operation presents no special difficulty on either side. Except for the rat, this is the animal in which the operation is easiest. In all the animals, adrenalectomy is simpler on the left side than on the right.

We believe that not nearly enough attention has been given to the proximity of great numbers of sympathetic fibers and ganglions which are liable to be crushed and torn unless the operator knows the importance of inflicting on them as little injury as possible. The removal of the adrenal glands or of one of them, unless it is done with care, is apt to cause a fall of blood pressure which has nothing to do with the loss of epinephrine previously discharged from the gland; it is,

instead, the expression of a shock-like condition apparently due to the traumatization of these numerous sympathetic fibers. We have often seen this in acute experiments in which the adrenal glands were removed to test the effect on some reaction which was previously obtained. When this shock-like condition supervened, such a reaction as acceleration of the "denervated" heart or vasoconstriction of a denervated limb on stimulation of sensory nerves might disappear, since shock was, of course, unfavorable to eliciting the reflexes. If the blood pressure later recovered with the adrenal glands removed, the reaction might again be obtained. It had not been suppressed because of loss of the epinephrine but on account of the shock caused by the trauma. In view of the fact that no other factor has been responsible for errors in work on the adrenal glands to the same extent as inadequate surgical measures, no apology is required for spending some time on the matter.

SYMPTOMS FOLLOWING ADRENALECTOMY

We return to a consideration of the consequences of complete adrenalectomy, which can be studied perhaps most satisfactorily on the dog. A short time is required for a dog to recover from the anesthetic. One of the advantages, probably not a slight one, of extensive experience in performing the operation is that the duration of the anesthesia can be diminished. The ordinary time of the operation with us is from eight to twelve minutes in a dog, and about five minutes in a cat. By that time, the skin is stitched and the anesthetic discontinued. It is, therefore, not to be wondered at that in a half an hour, sometimes less, the dog has generally recovered and is willing to eat, though not permitted to do so. The period of good health is proportional to the total period of survival, so that whether the latter is long or short, about the same number of days elapses between the first development of serious symptoms and death. During the period of good health the animal appears perfectly normal. It preserves habits or tricks which were characteristic before the removal of the second adrenal gland. It is impossible to determine from the animal's behavior whether it has lost its adrenal glands or not. Appetite is unaltered. Dogs that ate voraciously before loss of the adrenal glands eat voraciously after the glands have been excised; those which ate slowly continue to eat slowly. Dogs that liked meat still do so, and dogs previously fond of bread and milk continue to like this ration. The blood shows no changes so far as they have been looked for. The specific gravity, the red cell count, the hemoglobin percentage, the conductivity of the blood and serum, the relative volume of corpuscles as compared with serum, the nonprotein nitrogen, the urea nitrogen, the so-called "undetermined fraction" of the nonprotein nitrogen, the uric acid, the creatinine and the amino-acid nitrogen are not altered, except that in

some cases an increase in the nonprotein nitrogen, urea nitrogen, "undetermined fraction" and relative volume of erythrocytes may be detected a day or so before the first definite refusal of food.

Anorexia is the first and most constant of the serious symptoms which terminate the period of good health. Once declared, it persists, except that occasionally an animal after finally refusing the usual ration may be tempted to eat once, rarely more often, something which it considers a delicacy. Refusal of food is, of course, a common symptom in any sick animal. It cannot be said that there is anything especially characteristic about the anorexia of adrenal insufficiency, except that it is inexorable and that it presages the death of the animal in, at the most, a few days, usually two or three. To an observer who does not know that the adrenal glands have been removed, there is nothing which distinguishes this anorexia from any other anorexia, unless it is an aversion to fat which develops before total anorexia has set in. This point will be considered in connection with the changes in the pancreas, and again in connection with the aversion to fat seen in cases of Addison's disease. The anorexia may be accompanied by emesis. Bile may be present in the vomitus. As a rule the animal does not appear seriously ill at this stage. It is constantly a source of surprise to the observer until he gets accustomed to it, how slight an ailment adrenal insufficiency usually appears to be in a dog, at least until near death. It is the uniform and rapidly fatal result which shows that the symptoms, whether slight or not, are indications of a serious disturbance.

Asthenia, which has been emphasised by some authors as the chief and earliest symptom, is not as a rule obvious for some time after the animal has definitely refused food. The error is due to the fact that moribund animals were observed, dying mainly as a result of the operation. Naturally, dying animals are weak. Often the animals are strong on their feet, pugnacious if they were so before, and able to run well if they can be coaxed to try. They are, however, apt to be lethargic; as time goes on, the lethargy deepens into stupor and coma. Convulsions are sometimes seen. On the whole, however, the behavior of the animal after anorexia and the other symptoms have developed often by no means suggests danger to an inexperienced observer. The arterial blood pressure (systolic and diastolic) is not affected by the removal of the adrenal glands, as shown in dogs and rabbits by Rogoff and Dominguez by means of the carotid loop method of van Leersum. The pressure was taken at frequent intervals beginning before the removal of the first adrenal gland. Even during the operation, pressure readings were made, as stated, without revealing any change beyond the limits of the ordinary variations. The fall of blood pressure so commonly seen in Addison's disease is, therefore, not reproduced in experimental

adrenal insufficiency, probably because the latter condition is not sufficiently chronic. Undoubtedly, when the animal's circulation has become impaired, as commonly happens when death approaches, there is a fall in blood pressure. It has often been remarked that the pigmentary changes so characteristic of Addison's disease are not found in experimental adrenal insufficiency. One could not expect to find them in animals living only a few hours or days, or, on the other hand, in animals living on indefinitely because of the retention of sufficient interrenal tissue to maintain life. The picture seen in dogs deprived of their adrenal glands is, accordingly, not quite the same as that seen in diseases of human beings. It must be remembered that in Addison's disease the loss of the interrenal tissue is usually gradual as the pathologic process spreads. Sometimes it is apparently due to atrophy or, perhaps to congenital deficiency of the tissue, the glands being represented at necropsy by a few small nodules of the same structure as the cortex.

CAUSE OF THE SYMPTOMS AND DEATH

When the question arises as to what causes the symptoms and death in experimental adrenal insufficiency, it must be confessed that at present no definite reply is possible. It must be assumed that an intoxication develops, perhaps creeping on from the first day although not announced for some time by detectable symptoms. The remedial effect of large intravenous injections of salt solutions (Ringer's solution with dextrose) is scarcely to be explained except on the supposition that an intoxication has been produced, through the lack of a substance or substances elaborated by the cortex which prevents such intoxication, or of something which aids in neutralizing the toxic products and rendering them harmless. The increase in the nonprotein and urea nitrogen of the blood and in the "undetermined fraction" of the nonprotein nitrogen, and the diminution in the ratio of plasma to corpuscles, however related to the loss of interrenal function, advance in equal measure with the terminal symptoms. They may, as already mentioned, overlap by a day or so the latter part of the period of good health. The concentration of the blood sometimes becomes extreme, as many as 10,000,000 erythrocytes to the cubic millimeter being present, with the specific gravity of the blood exceeding 1.070. The concentration does not affect the serum, its specific gravity rarely exceeding 1.025 and its protein content being unaltered. The serum calcium usually undergoes an increase at the time of, or sometimes a little before, the development of the serious symptoms, especially anorexia, which terminate the period of good health. The blood sugar remains within the normal limits till near death, when a moderate diminution may occur. The uric acid of the blood undergoes no important change. The creatinine and amino-acid nitrogen sometimes show a small increase. The blood chlorine often undergoes a moderate diminution.

If metabolic or other derangements begin immediately or soon after the removal of the second adrenal gland, they have not yet been discovered. It may be that defensive, neutralizing mechanisms are at work which, for a while, are capable of dealing with the poisons, but ultimately break down. Later on, evidence will be given that the interrenal tissue contains a substance which, when administered to adrenalectomized dogs can lengthen the period of survival beyond anything seen in the control series. If this substance is a hormone normally given off by the gland, it may act by influencing the function of some of the important organs which fail sooner or later in its absence, or it may influence special metabolic processes. Then these organs or processes will be interfered with, and in addition poisons may be produced. Thus, in the case of the internal secretion of the pancreas, insulin supplies something necessary for the normal metabolism of carbohydrates, but in its absence toxic substances are also produced which are responsible for such symptoms as coma. The administration of insulin prevents the development of these poisons by restoring normal metabolism.

In one endocrine organ after another—thyroid and parathyroid glands, pancreas (islets) and interstitial tissue of gonads—active substances have been discovered which substitute for the glands. Even the adrenal medulla, the chromaffin tissue, perpares and discharges into the blood a specific substance, epinephrine which, although of slight physiologic significance, belongs to the group of hormones. Analogy suggests that the adrenal cortex or interrenal gland prepares and liberates a hormone also. To this substance the name interrenalin is given, although it has not yet been isolated.

The question at once occurs: Why do some dogs live much longer than others? No definite answer can be given, but one or two suggestions may be made. It is possible that some dogs have a larger store of the active substance than others, if the substance is stored in other tissues than the interrenal glands. This is on the assumption that it is manufactured solely in the adrenal glands. If so, it may be taken up and stored in other tissues, possibly in the interstitial cells of the gonads or, in the case of the female, in the elements from which the corpus luteum is developed. If that is the case, some dogs may store more than others and, therefore, have more at their disposal when the second adrenal gland is taken out. Then these tissues, the origin of which is probably similar to that of the interrenal tissues, may normally elaborate interrenalin, although it may not be liberated in the absence of any need for it. If liberated it would naturally constitute a small contribution compared with that of the adrenal glands. Another possibility is that some dogs may use up any store of the active substance with greater economy than other dogs. Finally, there may be no store whatever, but the resistance of some dogs to the consequences of loss of the adrenal

glands may be greater than that of others, just as the power of resistance to a disease or a poison may vary. None of these suggestions, or others which might be made, have been tested. The fact, however, that a range of from three to five days to fourteen days or more exists in the period of survival of dogs which possess no interrenal tissue invites speculation. Could the meaning of this variation be understood, much light would probably be thrown on the general problem of interrenal function.

POSTMORTEM OBSERVATIONS

The postmortem observations on dogs dying of adrenal insufficiency present some points of interest. The most constant change observed is congestion of the pancreas, usually intense and seldom absent. In cats and guinea-pigs, this is also a practically constant feature, although, perhaps from the small size of the organ, the pancreas is not so red. In all these animals, we have compared the postmortem observations with those in normal animals, and the difference is marked. The meaning of the congestion is unknown, but it would suggest some involvement of the organ due to the loss of the interrenal function. It cannot be stated at present how early this congestion is present; it is possible that it is only a terminal event, developing, perhaps, at about the same time as the anorexia or even later. In animals that have been examined microscopically, it appears to involve both acinar tissue and islets. To what extent, if at all, the secretion of pancreatic juice is affected by the changes in the pancreas, it is at present impossible to say. The loss of appetite for fats at a time when lean meat is still picked out and eaten may be connected with an impairment of the fat-digesting power of the pancreatic juice. In cases of well marked hemorrhagic congestion, the condition of the mucosa of the intestine would itself interfere with the digestion and absorption not only of fats but of other foods. Another striking appearance, although not so constant, is hemorrhagic congestion of the mucosa often associated with the presence of blood in the lumen of the gastro-intestinal tract. Sometimes intense congestion, with hemorrhage into the mucosa and blood in the lumen, is seen throughout the whole gastro-intestinal tract from the cardiac end of the stomach to the anus, but often only a portion or scattered areas of the tract are affected. Bile is nearly always found in the stomach. The esophagus never exhibits any congestion. It is occasionally present in the vermiform process and often in the the cecum. In exceptional cases, there is neither congestion of the mucosa nor blood in the lumen. It is probable that the gastro-intestinal congestion is a rather late event, but there is no exact information on this point. It may be present, however, some days before death; blood is sometimes passed from the rectum. The significance of these pathologic changes in dogs dying

of adrenal insufficiency is unknown; only they are often so extensive and severe as of themselves to constitute a sufficient cause for the fatal result, and, of course, if present early enough, for the onset of the characteristic anorexia. The congestion in the gastro-intestinal tract and in the pancreas is not merely a part of a general passive congestion of the viscera due to failure of the heart, for it may be extremely marked when the spleen, kidneys and other organs are only moderately or not at all congested. We do not desire to emphasize unduly the gastro-intestinal appearances, for it is known that in other conditions somewhat similar appearances may occur. In cats dying after adrenalectomy these changes, although often seen, are not usually so intense.

We have suggested the possibility that the gastro-intestinal mucosa may share in the elimination of the poison or poisons developed in adrenal insufficiency and may itself be finally crippled by the poison. An alternative hypothesis is that the cortex produces a hormone necessary, among other actions, for the continued normal functioning of the mucosa and also of the pancreas. In the dog, the appearances suggest that a disturbance of function centering around the alimentary canal is one of the consequences of adrenal insufficiency. That there should be no hemorrhage or hemorrhagic congestion in some of the dogs is, of course, no proof that the gastro-intestinal tract continues to function normally. The persistent anorexia and not uncommon emesis may be primarily due to gastro-intestinal changes not necessarily evidenced by congestion. The gastro-intestinal mucosa may be just as much a point of attack in the cat and guinea-pig, and in those dogs which do not show the appearances in question, as when the striking hemorrhagic changes are present. It is not worth while discussing at present whether the smaller dimensions of the structures, possibly even differences in the quantity or quality of the residues of food in the gastro-intestinal tract, may have a bearing on the matter.

THE CAUSES OF THE BREAKDOWN

It has been said that during the period of good health the adrenalectomized dog seems normal in every respect. Nothing suggests that the condition of the animal is serious and, indeed, hopeless. Is this appearance of perfect health fallacious? Are changes already in train which will soon issue in unmistakable symptoms? These questions cannot be avoided, but neither can they be answered at present. As already stated, search has been made by us for changes in the blood which might indicate that something was amiss, perhaps soon after removal of the second adrenal gland, although no visible symptoms had yet developed. Hitherto, all the results have been negative. Only when the train of symptoms appears which indicates that the period of good health is over do recognizable changes in the blood develop; these usually

increase until death. It is clear enough, however, that none of the changes in the blood studied by us follow soon after the loss of the interrenal function. If a poison begins to accumulate from the outset, although causing no symptoms until it has reached a certain concentration, requiring maybe a week or more, its detection is not likely to be easy. All we can say at present, therefore, is that during the period of good health the animal runs along on whatever reserves of interrenalin it possesses, if it possesses such reserves till in a week, more or less, the derangement of function leads to symptoms. If poisonous substances, produced in the absence of the interrenal tissue, are being eliminated or neutralized, it is possible that the period of good health is terminated by the breakdown of the organs concerned, perhaps owing to the harmful effects of the poisons on their own cells. At one time, it was suggested by certain writers including the author that the kidney might possibly be such an organ.

While no exact study of the kidney has been made, such observations as we have accumulated do not indicate that in the dog the kidney is specially concerned. The occasional pathologic changes seen in one or both kidneys are probably no greater than would occur in any large series of normal dogs. In rabbits, interference with a kidney at operation may account for some of the cases of renal change. We are far from regarding the pathologic appearances in the dogs' gastro-intestinal tract as proof that the mucosa takes a leading part in the elimination or neutralization of poisons produced in the body in the absence of the interrenal tissue. Nevertheless, it is well known that the mucosa can take an important place as an excretory organ under certain conditions; for example, when saline solutions are injected into a vein. It was shown by Sherrington long ago that much of the salt solution passed rapidly into the lumen of the intestine and was then gradually reabsorbed into the blood and eliminated by the kidneys. We have seen the same thing in experiments in which Ringer's solution was administered intravenously to adrenalectomized dogs. These experiments were undertaken to test the value of such injections as a therapeutic measure in adrenal insufficiency.

METHODS OF TREATMENT

As soon as we had accumulated a sufficiently large series of control dogs, it became possible to test methods of treatment. The only test which at present can be considered unequivocally positive is a prolongation of life decidedly beyond the maximal time seen in the control series. This is a severe test, as it involves the placing of the animal in such a position, through the treatment, that it can successfully meet not only one but all the emergencies which threaten its life. When positive, the test is for this very reason not open to doubt. It

would be much simpler to test the effect of a treatment on a characteristic symptom or on the concentration of a blood constituent, but we are not yet in a position to rely on such tests. Effects such as amelioration of symptoms also have positive value, even when temporary. Let it be repeated, however, that in drawing conclusions as to the efficacy of a treatment we have up to the present refused to accept as a positive result anything short of a decided prolongation of the maximal period of survival, and this in a large proportion of the cases. Some weight can also be given to the fact that a relatively large number of long periods of survival occurs in the treated series, though not necessarily beyond the maximum of the control series. Averages are of little use because of the large variations in the period of survival. They are quite misleading, of course, when they are derived from results obtained in only a small number of animals. A positive result of a given treatment must not be inferred from an apparent increase in the average time of survival unless the first test is positive, that is, unless a considerable number of the animals have lived well beyond the longest period of survival of the control animals.

Injections of Salt Solution.—As stated, injections of salt solution were one method of treatment studied. This was used for several reasons. If an intoxication develops at the time that the serious symptoms appear or is, perhaps, developing from the time of removal of the second adrenal gland, an irrigation of the poisoned tissues, including the blood, which would wash out the whole or a portion of the poison, is possible. A positive result would be that much evidence in favor of the existence of an intoxication; in addition, it would indicate that the poison, or an important fraction of it, was not yet firmly fixed. A salt solution was purposely chosen because its action would be understood to some extent and would be less complex than that of extracts of the glands. There could obviously be no substitution for the missing interrenal gland; nothing in the nature of a hormone could be supplied. Some dextrose was added, but it is not certain that this was of any importance. The intravenous injection of a salt solution is a feasible therapeutic measure; it was thought that if a certain amount of success was obtained in dogs it might well be considered, that in certain cases of Addison's disease, when the condition suggested intoxication and was in any case desperate, an occasional injection of Ringer's solution (in smaller proportional amount than for dogs) might not be justifiable and even promising. It was found that severe symptoms, such as coma and convulsions, could be temporarily ameliorated, and that in some cases animals might be rescued when moribund, and survive much beyond the maximal period of the control series. Further, it was shown that with daily injections of about 100 cc. of Ringer's solution per kilogram of body weight with some dextrose added, many dogs continued in good

health far longer than the maximal period among the control animals. The longest period of survival of dogs treated with Ringer's solution was 53⅔ days, nearly four times as long as the maximum period among the untreated control animals, and not much less than the average gestation period of dogs. Other survival periods among the seventeen treated dogs were 38, 33¼, 32⅔, 20 (two dogs), 19⅓, 19 and 17¼ days. Nine dogs (more than half of the total number) lived beyond the maximal period of the controls, and four additional dogs almost as long as the maximal period.

Nothing like these results was seen among the much larger number of controls. The results of the injections, therefore, were extremely good. It may be pointed out again that there are necessarily great difficulties to be overcome in adding perhaps forty days to the life of an adrenalectomized dog, which without the treatment would usually live only from six to ten days. It is not too much to say that the animal, although running along week after week as if the suprarenal glands were superfluous, is in reality in constant, and, after the ordinary survival period has passed, in imminent, danger of death. Nothing keeps it alive and, to all appearance, in normal health, except the daily liter, or whatever it may be, of a simple solution of salts, such as Ringer's solution. It is not even ascertained that the injection must be a daily one. Possibly less frequent injections would be better. The dose might also have been too large. It was impossible, even though a great deal of time was consumed in the investigation, to compare different doses, different salt solutions, different intervals between successive injections and different periods after the removal of the second adrenal gland for commencing the injections. There is no reason to suppose that we accidentally hit on optimal conditions. Our results are not the best which can be obtained. The unequivocally positive result of the test for lengthening the period of survival is sufficient proof of the beneficial effect of the treatment when carried on for long periods. Even more impressive although not susceptible of the same arithmetical comparison, is the immediate, almost startling, improvement often produced in animals the condition of which seems desperate, for example, in coma. This improvement may not last long in some cases, but in others the dog may take on a new lease of life. Obviously, the result must depend on the extent of deterioration. In one dog, for instance, convulsions and deep coma developed on the third day after the second operation. It was not expected to live through the night. It recovered, however, under treatment with salt solution, regained health and appetite and died on the thirty-fourth day. Symptoms such as anorexia, therefore, may sometimes be benefited, the animal picking up and beginning to eat again. But when the anorexia is absolute and has lasted for some time, this effect is probably rare.

The reason for starting the injections on the day after the second adrenalectomy, that is, long before symptoms of adrenal insufficiency had appeared, was theoretical, although not entirely so. It was thought that, if the injections washed out the poisons, the sooner they were started the better, so as to prevent the toxic substances, as far as possible, from anchoring themselves in vital tissues. Whether that idea is correct or not, it would seem reasonable to suppose that the injections, if beneficial, cannot be begun too early. The postoperative condition of the animal must, of course, be considered. As already stated, our animals recovered from the operation in a short time and were considered fit for injection on the following day. It must be said, however, that a few dogs may not stand so large an injection so soon after a serious operation. It is possible to produce serious effects in such animals, perhaps through dilatation of the heart. The heart's action and pulse should, therefore, be watched while the injection is proceeding. In a typical observation, the dog shows symptoms of increased activity of the bowel during or after an injection, and micturates copiously. If there is no micturition for several hours, suspicion should be aroused.

Administration of Cortical Extracts.—More directly concerned with the cause of death after loss of the adrenal glands and centering around the question of the existence in the cortex of an active substance capable of substituting for it like hormones of other endocrine glands, are our studies on cortical extracts, which have been going on for several years. As a method of treatment in adrenal insufficiency the administration of cortical extracts is, in some respects, the exact opposite of the injection of salt solutions. Yet the results on the lengthening of the period of survival are not very different.

From several of the endocrine organs, specific active substances have been obtained. In some cases it has been proved, in others it is assumed, that the formation of these substances and their liberation into the blood (or lymph) constitute the function of the gland. Assuredly the proof of the existence of these substances, in some instances followed by their isolation and their synthesis (epinephrine and thyroxin) and the determination of their constitution, has not been an easy task. But starting with the work of Baumann, Oswald and others on the active substance of the thyroid gland, followed by the demonstration, by Oliver and Schafer, that a vasoconstrictor substance can be extracted from the adrenal medulla (chromaffin tissue), it has gradually been shown that active principles can be obtained also from the pancreas (islets), from the parathyroid gland and from the sex glands. These have been proved capable of "substituting" for the glands which contain them, in the case of the thyroid gland and the islets of Langerhans, so that in their absence, or when there is undue reduction in amount or in func-

tional capacity, the artificial administration of thyroxin or insulin, respectively, replaces the deficient internal secretion. Important, even indispensable functions are clearly performed by these substances. The specific substance, parathyrin, formed by the parathyroid glands, the loss of which causes tetany, has also been obtained in extracts by Collip. The increase in the serum calcium (hypercalcemia) caused by its administration throws light on the previous discovery of McCallum that calcium salts prevent or cure tetany caused by removal of the parathyroid glands.

It may be mentioned that the largest parathyroid glands that we have ever seen were those of the adrenalectomized dog which lived longest (seventy-eight days) in the series of animals treated with extracts. We do not venture to suggest that the hypercalcemia often seen in these dogs, although only in the terminal stage or slightly preceding it, is brought about through the parathyroid glands. The relations of the adrenal glands, both interrenal and chromaffin tissue, but especially the latter, with other endocrine glands have often been assumed. Proof, however, is still lacking, save in one instance—the correlation of the interrenal gland and certain cells of the gonads (interstitial cells and the corpus luteum?). Since these tissues appear to be derived from the same embryonic structure, the correlation is easy to understand. Changes in the cortex following gonadectomy, and in the gonads following adrenalectomy suggest also the possibility of a functional connection. The best illustration of this is the influence of "heat" (and pregnancy) on the length of life in dogs after loss of the adrenal glands.

Hormones from the ovary and placenta have been described. One, at least, was partially isolated. Replacement effects have been demonstrated in ovariectomized animals, including congestion, swelling and other external signs of estrus (Doisy and other observers).

The adrenal medulla and the posterior lobe of the pituitary gland yield characteristic substances. While of great pharmacologic and therapeutic importance, it is unknown whether they have physiologic importance. It is not even ascertained whether solution of pituitary gives off the active substance to the blood. The question of the function of the epinephrine produced by the chromaffin tissue of the adrenal body will be discussed later in this paper. More or less specific actions, particularly in relation to growth, have been attributed by some observers to extracts prepared from the anterior lobe of the pituitary gland. As investigation proceeded, and as each gap was filled in, there was an increasing probability that the adrenal cortex would in time be added to the list. The discovery was retarded by the experimental difficulties.

No symptom or blood change was known to us which characterized the condition of adrenal insufficiency. We were unable to determine,

as for instance in the case of insulin, by a simple estimation of a blood constituent, the potency of any extract in counteracting the loss of function of the cortex. If this becomes possible, extracts can be tested much more simply than by determining how long animals survive when they are administered. The labor of bringing our experiments to the present point has been great. The work was planned and begun a good many years ago.

The investigations have culminated in the demonstration, for the first time, that cortical extracts can be prepared which can substitute for the adrenal glands. It was indispensable to prove this in order that further attempts to extract and purify the active substance or substances should be placed on a secure basis. The proof that we obtained such extracts is that among the dogs given intravenous injections of certain extracts (generally on alternate days), a considerable number lived far longer than the maximal period seen in untreated control animals. The volume of the injection was usually 1 cc., so that there could have been no irrigation similar to that assumed to result from an injection of Ringer's solution. We are left with the explanation that the extracts supplied something normally supplied by the interrenal tissue. For this we have suggested the name interrenalin.

As in the case of the salt solutions, it is not to be supposed that we attained optimal results with the extracts. Larger and more frequent doses might have been better, but this has not been ascertained. The important point is that we did find extracts and did administer them in doses which were clearly efficacious. The extracts were made from the adrenal glands of dogs or from the cortex of animals from a slaughter house. Probably each batch differed from the rest in the concentration of active substance obtained by extraction. We had no means of standardizing the extracts. Different dogs might have responded differently to similar doses of active substance, some requiring larger doses than others to stave off the fatal breakdown. The possession of a large series of control animals, however, prepared by an adequate technic, enabled us to conclude with certainty that the indispensable test, the lengthening of the period of survival, was strongly positive. The period of good health was correspondingly lengthened. Among the dogs which did not actually live longer than the maximal period for the controls, a larger number, apparently more proportionally than in the control series, attained the longer periods of survival. Occasionally an animal already beginning to go downhill seemed to be revived by a dose of extract, not immediately as in the case of the treatment with Ringer's solution but after some time. The serious symptoms, when they developed eventually in animals treated with extracts, often seemed to be milder than in the controls. The pathologic appearances seen post mortem were also thought to be less pronounced in many

cases. Let it be repeated, however, that at present we do not rely on these subsidiary tests. Our positive conclusion is based on the decided increase in the period of survival beyond the maximal recorded for the control animals. Since the treated animals differed from the untreated controls only in having received extracts, the lengthened survival must have been due to an action exerted by the extracts, which, it is to be supposed, supplied the material (interrenalin) naturally supplied by the cortex.

INFLUENCE OF "HEAT" AND PREGNANCY ON SURVIVAL

The interesting observation has been made by us that dogs in "heat" survive the loss of the adrenal glands much longer than the maximal survival period of the controls. All the dogs from which the second adrenal gland was removed during proestrum or estrus gave this result. One lived until the sixty-fifth day. The period of good health was correspondingly prolonged. The mechanism by which the consequences of total adrenalectomy are staved off must be different both from that of the administration of extracts and from that of the injection of salt solutions. The most plausible view is that changes in the ovary are concerned. The similarity in structure, and in the nature of the inclusions, between the corpus luteum and the adrenal cortex has often been pointed out.

The inclusions in the ovarian interstitial cells also resemble those of the cortical cells. In heat, the changes in the ovary, including the development of the corpus luteum, may render available, in sufficient amount to make up for the loss of the adrenal glands, the indispensable substance produced by the interrenal tissue. As the development associated with heat subsides, this supply must fail and the fatal consequences of adrenal insufficiency then develop. Of course, it is theoretically possible that the ovarian tissues act by destroying poisons produced in the absence of the adrenal glands. Actions of detoxication have been attributed to every endocrine gland until in one case after another a specific substance has been discovered which is necessary to the proper carrying on of particular functions. When that has been done detoxication ceases to be mentioned. It must not be forgotten, however, that when a metabolic process is no longer carried out in the normal manner in the absence of the necessary hormone, the abnormal or incomplete chemical reactions may give rise to the production and accumulation of substances which act as poisons.

Pregnancy, in dogs, is another condition in which we have observed longer periods of survival after adrenalectomy than in the control animals. Naturally in a condition associated in itself with formidable risks, not every animal shows a prolongation of the period of survival. Indeed, not a few succumb earlier than they would have, had they not

been pregnant. Yet it has been clearly demonstrated that many survive from 20 to 30 days, and some from 30 to 40 days. As long a period of survival as 58 days has been seen. One bitch lived for 57½ days. One of the pregnant animals survived for 46 days, one for 32⅔ days, one nearly 27 days and one more than 25 days. Since every pregnant bitch has necessarily been in heat, it cannot be said offhand to what extent pregnancy contributes to lengthening the period of survival. To settle this statistically would require a great deal of work. Heat causes a slight disturbance compared with pregnancy, and no risk. If the aforementioned view of the nature of the protective influence of heat is correct, it is to be assumed that the changes in the sex glands, proceeding further in pregnancy, are still more efficacious than in heat. The metabolic changes in pregnancy are also greater. If lactation has anything to do with the matter its effect will be added to the other effects of pregnancy. The adrenal glands of the embryo in utero do not appear to be concerned. They are certainly not indispensable, since heat is associated with a marked prolongation of the period of survival. Also, survival much beyond the maximal period in the control animals, has been seen in the pregnant bitch after delivery. In heat and pregnancy it is possible that changes in the uterus may influence the duration of life after total adrenalectomy.

Before leaving the subject of the action of heat and pregnancy, it should be remarked that the discussion is by no means academic. The proestrum or period of the blood-containing discharge in dogs is currently assumed to correspond to menstruation in women. The question will sometimes be asked by patients with Addison's disease, whether menstruation is unfavorable or not in this condition; in any case, it may have to be considered by the physician. Apart from the fact that menstruation may be disagreeable and depressing, especially in the early stages, some patients state that their general condition is distinctly better during menstruation. The question whether pregnancy should be avoided may not arise often, owing to the general condition of the patient. It may sometimes arise, however, or the patient may be pregnant; then there may be the question whether interference should be considered or would be profitable. It would be absurd to claim that our observations on dogs supply data sufficient to settle such questions. But such data as they do supply might be helpful in some measure.

It might be anticipated that in some cases a pregnant animal might react less favorably than a nonpregnant animal to removal of the second adrenal gland. Pregnancy itself being a handicap in certain respects, the surgical operation of adrenalectomy, or possibly the state of adrenal insufficiency may exert an unfavorable influence, so that the period of survival is shortened instead of lengthened. We have seen such instances in dogs. Occasionally, premature delivery may be caused by the operation, although this does not necessarily prevent survival for a longer period than the maximum seen in control animals. In one

dog, labor began half an hour after the operation and the animal survived for twenty-six days, nursing the pups normally. It has not been possible to demonstrate clearly any protective influence of pregnancy toward adrenal insufficiency in cats. Premature delivery is often the result of the operation, which apparently is borne worse by pregnant cats than by pregnant dogs.

It is unlikely that there is an essential difference between dogs and cats in regard to a potential protective influence of pregnancy, although it may be more difficult to demonstrate such an influence in the cat. More attention to the stage of pregnancy at which the second adrenalectomy is made might reveal a period when complications are least likely to occur; a positive effect might then be obtained.

DETOXICATING FUNCTION OF THE ADRENAL GLANDS

An assumed detoxicating function of the adrenal glands has been mentioned already. Those who have supported the idea of such a function have usually conceived of the detoxication as applying to many poisons, both bacterial toxins and drugs. Some have held that the cortex is the tissue concerned in this process; the majority of the authors, however, have considered it a function of the medulla. The evidence brought forward in support of the detoxicating function of the adrenal gland has generally been a supposed increase in the susceptibility of adrenalectomized animals to certain toxins or poisons. As in the case of nearly all other studies made on such animals, investigators have often been misled by their failure to appreciate the influence of unskilled surgical procedures on their results. Tests have been made frequently by introducing highly toxic material or depressing alkaloids into moribund adrenalectomized animals thus hastening death when it is already inevitable.

Claims have been made by a number of authors that animals deprived of their adrenal glands are much more susceptible to the poisonous effects of tetanus toxin and of morphine. A review of the literature may be found in papers from this laboratory by Rogoff and Ecker, and Rogoff and de Necker, who investigated the supposed increase in the susceptibility of adrenalectomized rats to tetanus toxin and to morphine. They found no evidence, in a large series of animals, of increased toxicity of these substances after removal of the adrenal glands. Many rats which had been operated on were able to tolerate practically the same doses of the poisons as were tolerated by control animals which had not been operated on. Fully three fourths of the deaths that result from double adrenalectomy in rats occur within a period of ten days beginning on about the fifth or sixth day after the operation. The administration of any poison during or preceding this period, as reported

by other observers, would obviously lead to the erroneous impression that the substance was more fatal than in control animals. Indeed, a harmless substance introduced during this period could be considered toxic if no consideration were given to the fact that the animal was moribund. When, however, these poisons were administered to rats adrenalectomized during the period of good health (that is, before or after the period mentioned), it was found that doses up to the minimal lethal dose for control animals were tolerated by many adrenalectomized rats. Rogoff and Ecker investigated the complementing activity of the blood serum in rabbits on which adrenalectomy had been performed and found no difference from control animals which had not been operated on.

That toxins, diphtheria toxin, for example, may poison the adrenal glands as they poison other tissues, is, of course, true. Some of them may even show a preference for the interrenal or the chromaffin tissue. A not uncommon reaction of the cortex to infections and intoxications is hypertrophy (or hyperplasia). But none of these facts can be taken as evidence of a special detoxicating function. Now that our investigations have proved that an active substance, extracted from the cortex, can greatly prolong life after total adrenalectomy, this substance (interrenalin) takes its place with the hormones produced by the other endocrine glands, and the function of the cortex is to produce it. The theory of detoxication was largely based on the desire to endow this gland with a function. Now that a function has been indicated and one of great importance, for a substance which preserves life cannot be insignificant, it is probable that the theory will retire into the background.

The last speculation on functions of the cortex which will be mentioned is that it is concerned with lipoid, especially the production of cholesterol, and governs cholesterol metabolism. There is little or no foundation for this theory. Cholesterol, of course, exists in the cortex in a relatively large amount, along with lecithin. The inclusions of birefringent lipoid in the cortical cells, especially in the spongiocytes of the zona fasciculata, are the most prominent microscopic features. They are picked out in polarized light by their property of double refraction. Their impressive appearance does not prove that they play an important rôle. The histologic picture is an uncertain guide as to their function and fate, although some cytologists are convinced that they represent a stage in a process of secretion which culminates in their extrusion into the blood. It cannot be said that any really crucial evidence has been furnished to support this conclusion. We ourselves can only contribute the fact that in our studies on adrenalectomized dogs no definite changes in the cholesterol content of the blood were made out.

THE ADRENAL MEDULLA

None of the endocrine glands produces an active substance better characterized than epinephrine. Its chemical constitution is understood. It has been prepared synthetically. Its physiologic reactions are numerous and striking. It is known to be found in the cells of the medulla. It is responsible for the brown color which the massive inclusions in the medullary cells assume in chromic acid or chromium salts. It has been proved to be given off to the blood, and it is the only substance of the group in which this has been clearly demonstrated. In numerous experiments on dogs, cats, rabbits and monkeys it has never been missed in the blood of the adrenal veins unless its liberation was purposely interfered with. Its passage from the cells to the blood is strictly under the control of nerves running in the major and minor splanchnic nerves and in branches from the lumbar sympathetic chain. When these are completely cut, no epinephrine is found in the blood of the adrenal veins, although the substance can still be found in the medullary cells. No symptoms are produced by section of the nerves supplying the adrenal gland. A temporary loss of weight may occur but this has no special significance. The animals remain in good health indefinitely. The same is true if the medulla is completely extirpated. It is, therefore, impossible to assign to the medulla any function indispensable to life, or, indeed, any function of physiologic importance. This has seemed disappointing to some authors; they have asked whether it is likely that an organ producing and discharging a substance capable of such striking reactions when administered artificially does not possess physiologic significance. One school of authors apparently accepting the view that under ordinary conditions not enough epinephrine is discharged to cause any definite effect, has put forward the hypothesis that in certain emergencies the output of epinephrine is markedly increased through stimulation of the secretory nerves of the medulla. Certain reactions associated with emotions are supposed to be brought about largely through epinephrine liberated by the adrenal glands. These reactions can be elicited by stimulation of sympathetic nerves and also by epinephrine in sufficient doses. The only question is whether sufficient quantities of epinephrine are liberated per unit of time, under the stress of these emotions, to raise the concentration of that substance in the arterial blood to the level at which stimulation of the structures involved will occur. If such quantities are liberated, it is scarcely necessary to verify the occurrence of the reactions.

We believe that there is no evidence that it makes any difference whether the adrenal glands are discharging epinephrine, are prevented from discharging it, or are absent: the reactions accompanying emotions are the same, quantitatively and qualitatively. We are therefore unable to accept the view that an important, or indeed a perceptible factor, in emotional expression is an increased output of epinephrine.

CHANGES IN OUTPUT OF EPINEPHRINE

The same considerations apply to the supposed increase in the rate of output of epinephrine caused by stimulation of certain afferent nerves and by general asphyxia. If the rate of liberation of epinephrine is sufficiently increased, any of its physiologic reactions can of course be obtained. In experiments, however, which permitted a quantitative estimation of the epinephrine given off per minute by the intestine segment method, we were unable to find any increase either during stimulation of the central end of the sciatic, the brachial or the splanchnic nerves, or during asphyxia. Stimulation of the peripheral end of the splanchnic nerve caused a large increase, as much as twentyfold, whereas excitations of the central end, interspersed among the stimulations of the peripheral end, had no effect on the rate of output. Numerous reflexes were elicited by the stimulation of the central splanchnic nerve, while it failed to affect the output of epinephrine. We have repeated these experiments on afferent stimulation in several researches, always with the same negative result; and similar results were obtained for asphyxia. Acute cerebral enemia, however, caused by tying off the arteries going to the head, excites an increased output of epinephrine, as was first demonstrated by Rogoff in this laboratory.

It would be inappropriate to use the present occasion for controversial purposes. The only reason for mentioning that our results on certain points differ from those of some other investigators is that the discrepancies involve points of technic, including operative technic, which have been found to influence greatly the consequences of adrenalectomy. Differences in the results of experiments on the survival of animals which always die after removal of the adrenal glands depend essentially on differences of technic, including of course preoperative and postoperative care. The decision must always be in favor of the investigator whose animals live longest, assuming, of course, that adrenalectomy was complete and accessories were absent. There is no reason why discrepancies in the results of acute experiments should not also be due to differences in the operative work. If one observer, for instance, fails to obtain a reaction (for example, acceleration of the denervated heart or shrinking of the denervated limb on stimulation of the sensory nerves) when the adrenal glands are eliminated, while another succeeds in obtaining it, the decision must be in favor of the latter who has been able, by better technic, to eliminate the glands without abolishing the reaction. The best method is to perform the operation, partly or wholly, some time before the experiment, which is made after complete recovery from the operation. In any case, we consider that extreme care must be exercised in removing the adrenal glands. Clipping off the veins tightly enough to prevent passage of blood from the glands is the least harmful procedure for those whose

experience in these operations is not extensive. This does not abolish the reaction of the limb caused by stimulation of the sciatic nerve, although it can be verified that the block on the adrenal veins is complete. The same considerations apply to operations on the adrenal glands in the experiment on the denervated heart. The crucial test is to perform the experiment after proper elimination of the glands. We have obtained the reactions, often in undiminished intensity, in their absence. It is, therefore, impossible for us to believe that it is correct to attribute the reactions solely to the reflex discharge of epinephrine. If the reactions can be typically elicited with the glands lying in a dish, the adrenals are not essential to their production.

The positive observations on the influence of sensory stimulation and of asphyxia reported by certain Japanese observers who used our intestinal segment method, have been thoroughly considered and checked by us. We may report on this matter in another paper. We have no hesitation in stating that their conclusions are based on an imperfect application of the method. Their values for the concentration of epinephrine in the blood of the adrenal veins and, therefore, in the outputs, are loaded with a serious error which makes them much too great, incredibly great to us, in many instances. We believe that this is due to the cumulative effect of more than one mistake in the application of the method. In some cases, acceptance of the nominal concentration of epinephrine in the standard instead of the real concentration may be a factor. Material loss of epinephrine from solutions made up at the beginning of the test and kept standing, with frequent opening and introduction of pipets into the bottles, can occur. We make up each specimen of epinephrine just before application to the segment. If an error of this nature is made, the effect will be to increase the apparent concentrations (and outputs), and the observer who obtains the smaller concentrations may be presumed to have avoided error from this cause more successfully than he who obtains the larger concentrations. When one of the Japanese observers finds a concentration of 1 : 250,000 in the initial sample of blood from a dog, weighing less than 12 Kg., with a flow of blood of 30 cc. per minute from the adrenal glands, we can only say that there is a big error somewhere. We have never seen any condition like this in the large number of dogs on which we have made estimations. The output for the animal per minute is 0.12 mg. of epinephrine (the observer gives it as 0.012 mg., but this is obviously an error if the concentration is given correctly). If this output were maintained for eight or ten minutes only, an amount of epinephrine equal to the entire store in the glands would be given off. He does not point out this amazing result or make any comment on it; it simply goes down in the table. When another of the Japanese investigators finds in a cat a concentration of 1 : 40,000 in the blood of the adrenal vein, probably about

1:20,000 in the serum (after nicotine), no suspicion is betrayed that results of this kind tend to discredit the paper. Yet in discussing reports of other authors on perfusion experiments with the adrenals of oxen (a poor method for studying the secretion of epinephrine) a point of exclamation is inserted by the observer when he mentions that concentrations of from 1:100,000 to 1:20,000 (!) were found in the perfusion fluid. The point (of exclamation) is well taken. In a deafferented dog, that is, one in which the posterior roots supplying the operative field have been cut, a concentration of 1:70,000 was found in the initial specimen of blood, with a correspondingly large output. Nothing like this was found in the rest of the experiment, even when sensory nerves were stimulated. The explanation given is simply that the dog was excited and objected to being fastened. No such concentrations and outputs were found in initial specimens from other dogs of the series which behaved in the same manner. There are numerous records of excessive concentrations in practically every table in the series of papers, concentrations such as we have not seen under similar conditions, and many of which could be estimated by a colorimetric method. In our own investigations, it was only when the output was greatly stimulated (by nicotine) that concentrations capable of being estimated colorimetrically were seen, although they were much smaller than those given by the Japanese investigators. On internal evidence, therefore, we must decline to accept the results of these workers; we object as strongly to the figures by which they profess to confirm our work (strychnine, nicotine, etc.) as to the figures on which they rely when they come to conclusions different from ours (sensory stimulation and asphyxia).

Other observers who have obtained what they consider positive results have used methods which did not permit estimation of the rate of output of epinephrine or of changes in that rate (anastomosis of the adrenal vein of one dog with the jugular vein of another, etc.). Their conclusions are based on the occurrence of one reaction or another which they interpret as indicating an increase in the output of epinephrine during sensory excitation or asphyxia. But without exception the supposed demonstrations fail to show that the output is increased. A great defect in these methods is that changes in the rate of blood flow from the adrenal gland and the rate of passage of epinephrine into the reacting animal are not controlled.

ACTION OF DRUGS ON THE OUTPUT OF EPINEPHRINE

The action of certain drugs, first investigated by us, on the output of epinephrine has been mentioned incidentally. It deserves fuller treatment for its physiologic interest and, in some instances, because of a possible therapeutic value. Space is not available, however, for

a detailed discussion. It will suffice to say that some drugs increase the rate of output, for example, strychnine. The increase may be to many times the initial value, and the arterial blood may become charged with detectable concentrations. The action of strychnine is central; section of the splanchnic and other nerves going to the adrenal glands prevents it. An increase to 100 times the original (diminished) output in an animal with a high section of the cord has been seen on administering strychnine. Morphine (in cats) and physostigmine are other drugs which increase the output.

Other drugs diminish the output of epinephrine. Nicotine is an example. The paralyzing action is preceded by a brief period (from half a minute to a minute) during which the output is greatly increased. The increase swings over quickly into a marked decrease, which lasts much longer but can end in a recovery if the dose is not too great. The stimulating action can be elicited after the splanchnic nerves, etc., have been cut; it is, therefore, not a central action.

A large number of drugs may be expected to exert an action on the output of epinephrine. We investigated a considerable number and had planned to examine a good many additional drugs likely to be found active, but the work on the cortex came to the point at which all our available time was absorbed. It was necessary to abandon further work on the action of drugs on the output of epinephrine at least for a time. Whether such an increase as can be caused by strychnine and other drugs would ever be useful could only be determined by experience. Calculation, however, of the greatest possible effect of safe doses on the output might indicate whether the corresponding increase in the concentration of epinephrine in the arterial blood would be of any use in certain conditions. It is easy, of course, to introduce artificially far greater amounts of epinephrine than can ever be given off from the glands. Usually the results have been disappointing. That epinephrine should have no substitutive effect in experimental adrenal insufficiency, as shown by us many years ago (for the first time, we believe, on properly prepared animals), and in Addison's disease, is to be expected since the loss of the cortex is the important lesion in these conditions.

COMMENT AND SUMMARY

Our first step was to show conclusively that the interrenal tissue (cortex) is the part of the adrenal body indispensable to health and life. The chromaffin tissue (medulla) can be destroyed, the discharge of epinephrine from it arrested by section of its nerve supply, or both operations can be performed without ill effect, immediate or remote, and, indeed, without any noticeable effect.

We then studied the symptomatology and pathology of the condition which follows complete adrenalectomy (total adrenal insufficiency)

and determined the length of the period of survival and the period of good health in a large series of dogs, destined to serve as controls for our studies on the influence of treatment by cortical extracts and in other ways. Nothing in the literature was found to be of value, because it was clear that the animals had died largely in consequence of inadequate operative technic and seldom, if ever, from adrenal insufficiency alone. Our results proved that dogs properly operated on, and under proper conditions, lived in a majority of the cases from 6 or 7 to 8 or 9 days. A good many survived well into the second week, and not a few lived for 13 or 14 days. Occasionally a dog lived a day or two longer. The average for the first 120 dogs was 7 days, and for the later series about 8 or 9 days.

Cats live longer than dogs, the average period of survival in our series being 11 days. Many cats live for 2 weeks; a few 3 weeks. Occasionally an animal survives longer than the fourth week. One lived for 32½ days.

A series of animals in which treatment is given (for example, with extracts), in order to yield a definitely positive result, must show a fair number of animals surviving well beyond the maximal periods of life in the control series; also, a considerable number should reach the longer periods of survival of the control animals. A comparison of the averages is not at all satisfactory unless the tests mentioned give strongly positive reactions. If a series of treated cats were to show a few animals living from three to five weeks and many of them living from nine to fifteen days, this could not be regarded as a positive result. Similar results for dogs, however, would be considered positive. Since the comparison depends absolutely on the control animals, too much care cannot possibly be taken in accumulating a good control series.

We have shown for the first time that extracts of cortex, from the adrenal glands both of dogs and of animals from the slaughter-house, cause prolongation of life when injected into dogs, far beyond any results seen in the control animals. The period of good health is correspondingly prolonged. The interrenal tissue therefore contains and, it is to be supposed, produces a substance which we suggest may appropriately be termed interrenalin; and this substance has the power of staving off death in adrenalectomized dogs. As soon as the difficulty of this feat is realized, the question whether life can be prolonged ten days, fifty days or hundreds of days ceases to take first place. The problem becomes a matter of dosage, the preparation of the extract, etc. If life is prolonged beyond a doubt by the action of an extract, the active substance in some way or other must enable the organism to surmount all the emergencies which threaten its life and will inevitably destroy it when it has reached the span, brief at best, allotted to dogs deprived of the adrenal glands and not subjected to

treatment. It is not a small reaction of an unimportant substance which neutralizes the poisons destined to overwhelm the untreated animal within a week or two, or prevents their development by contributing to the metabolism what is necessary to keep it normal; nor is it a small reaction of an unimportant substance which staves off the breakdown, probably centering about the gastro-intestinal tract, and announced first of all among the serious terminal symptoms by the onset of anorexia. It is a potent reaction of a highly significant substance that takes hold of a dog destined to die, let us say at the end of the tenth day, and carries him on in good health until the end of the twentieth or thirtieth day, or sometimes much longer. The test is, indeed, so severe that it ought not to have occasioned disappointment had the series in which treatment was given rarely revealed an animal living longer than any of the controls. There would still have been good reason to believe in the existence of a cortical hormone and the possibility of substitution of it for the missing interrenal tissue. Clear and definite proof, however, which must be accepted by everyone would not have been obtained. It is quite another thing to study a symptom not in itself acutely fatal in order to see whether treatment with extracts has any effect on it. This could be done with insulin by estimating the sugar content of the blood, but nothing of the kind is possible, at present, in the case of the active substance of the cortex. It is true that we have gained the impression that some of the symptoms, especially the anorexia and what often characterizes it, the aversion to fats, may be modified by treatment. But this is too vague to serve as a crucial test. Nor does it seem possible at present to employ the development of the increase in the nonprotein nitrogen, the urea nitrogen, etc., as a test of the efficacy or inefficacy of a treatment, for the change occurs when the severe terminal symptoms appear or are about to appear; when these symptoms show themselves there is no reason for troubling about less evident changes.

It would be premature to attempt to decide at present what the function of "interrenalin" is. Pharmacologic studies may throw some light on the question. Its influence on the general metabolism or on some special metabolic process must, of course, be investigated. The fact that in the untreated animal, as has been mentioned, the breakdown seems to center around the gastro-intestinal tract and that the pathologic changes are prominent there suggests that the cortex has some special relation to that tract, including the pancreas. In Addison's disease, gastro-intestinal symptoms are among the classic features. We have seen at autopsy in a case of acute adrenal insufficiency a condition (gastro-intestinal congestion, hemorrhage, blood in the lumen and congestion of the pancreas) precisely resembling what is so often observed in dogs dying after loss of the adrenal glands. The necropsy showed destruction and atrophy of the glands. The relationship, however, is not asserted; it is

merely suggested as a hypothesis. It is uncertain whether the asthenia, which develops sooner or later following the appearance of anorexia, is so specific that the cortex must be assumed to bear a special relation to the neuromuscular system.

Whatever the function of the cortex may be, the artificially administered extracts substitute for it, so that the animal, so far as is known, remains entirely normal. It is possible, however, that even from the first day, cumulative changes occur, although they escape detection, which in the long run, culminate in the abrupt appearance of the terminal symptoms and death.

If it is the office of the cortex to contribute to, perhaps to control, the functioning of certain tissues or organs or certain metabolic processes, these will, of course, suffer derangement after removal of the adrenal glands. In addition to the loss of these functions and, of course, connected with it, the development of metabolic faults or faults of intestinal absorption may lead to the accumulation of poisons. In fact, a marked feature in animals dying of adrenal insufficiency is an intoxication, usually revealing itself some time after the anorexia has appeared, deepening as the end approaches, and finally submerging the central nervous system and affecting the circulation. One can think of loss of the cortical active substance, therefore, as influencing the organism in two ways: derangement of the mechanisms or processes which it normally controls, and the development of poisons owing to that derangement. These two factors are not mutually exclusive. An analogy may be found in diabetes. Lack of insulin not only interferes with normal carbohydrate metabolism, leading to an increase in the sugar content of the blood, but also leads to the accumulation of substances associated with the deranged metabolism, which may cause diabetic coma. That an intoxication is present in total adrenal insufficiency is, in any case, certain. The condition can be relieved, as we have shown, by the intravenous injection of salt solutions. These obviously cannot supply a hormone, and may act by washing out injurious substances. Dogs have been kept alive by this treatment for as long as fifty-four days after removal of the second adrenal gland. Many lived far beyond the maximal period seen in the controls. Some were rescued after serious symptoms (for example, coma) had developed, and survived for many days thereafter.

It is shown that no function indispensable to life is performed by the medulla. Indeed after the destruction or denervation of the medulla, or both, everything goes on as before; the animal lives on indefinitely in good health and is indistinguishable in its behavior from an animal which possesses its adrenal chromaffin tissue. One deduction from this fact is that there is no foundation for the view, almost invariably expressed in clinical writings, that Addison's disease is due to loss of

epinephrine. Some physiologists, on the strength of ambiguous observations interpreted as indicating a reflexly increased output of epinephrine, have unduly stressed, we think, the importance of the part played by the medulla in vascular reactions and in the reactions associated with the expression of emotions. If no change is caused by elimination of the medulla, epinephrine from the medulla does not exercise important functions.

A detectable content of epinephrine has always been found by us in the blood of the adrenal vein, although too small for detection in the arterial blood owing to the great dilution. The output of epinephrine is much increased by stimulation of the peripheral end of the splanchnic nerves, according to our quantitative confirmation of previous workers. It is greatly diminished or abolished by section of the nerves going to the adrenal glands. Whether the epinephrine secretory nerves regenerate after section cannot be stated definitely; after many months, the output of epinephrine is still much diminished. The concentration of epinephrine in the blood of the adrenal veins is approximately in inverse ratio to the blood flow, so long as the flow is not too small. The output is markedly increased by certain drugs, for instance, strychnine, physostigmine and, for a brief time (usually a minute or less), nicotine. It is diminished by other drugs, such as nicotine (following the brief increase). It is increased, although not beyond the maximum of the ordinary output (in cats), by acute cerebral anemia.

The foregoing observations have been confirmed by subsequent investigators. While we have been unable to measure a clear difference in the output of epinephrine during the excitation of sensory nerves or during general asphyxia, some other observers claim to have done so.

It may be asked, what then is the function of the medulla? In the past, errors have been made in attempts to provide this gland with a function. I should be loath to conclude that it is the "roi fainéant" of the endocrine glands, a kind of personage little known to physiology. To say that it must be doing something, is a proposition which surely is not worth while contradicting. It may even appear self-evident to some. The real question would be, is it doing anything worth while, anything that can properly be spoken of as a function? Does it keep up the blood pressure? The blood pressure, however, is not altered, either during or after removal of the glands. The point of view is sometimes shifted by the assumption that the extracapsular chromaffin tissue is doing the same thing as the medulla, turning out the necessary epinephrine, and that epinephrine is not lacking after elimination of the adrenal glands. Those who believe that reactions, such as those previously mentioned, are abolished when the glands are eliminated, can hardly acquiesce in this conception. There is experimental evidence against it. When more is known of the formation of epinephrine and

its forerunners, new light may be thrown on the question under discussion. We cannot accept lightly the view that the medulla has no physiologic function, but is important only as raw material for the manufacturing druggists.

There is evidence that in certain forms of experimental hyperglycemia, epinephrine from the adrenal glands may be a factor, although usually a minor one. Thus, puncture at a certain part of the floor of the fourth ventricle causes hyperglycemia and also an increased output of epinephrine. The hyperglycemia is well obtained when the adrenal medulla has been eliminated, and is dependent on splanchnic nerve fibers going to the liver. How much it is aided, if at all, by the increased output of epinephrine, dependent on splanchnic nerve fibers leading to the adrenal glands, depends merely on the rate and duration of the increased output. If the concentration in the arterial blood is increased beyond the threshold value needed to cause epinephrine hyperglycemia and is maintained above this value long enough, a part of the effect will be due to the epinephrine. The hyperglycemia associated with asphyxia does not seem to have an adrenal element. No difference has been found in the amount of the hyperglycemia whether the medulla was eliminated or not. On the other hand, the hyperglycemia caused by morphine (in cats and dogs) is greatly diminished or abolished when the adrenal medulla is eliminated. Such observations suggest, although they do not prove, that epinephrine may exert some influence on carbohydrate metabolism. But it must be remembered that, so far as we know, the concentration of epinephrine in the arterial blood never under physiologic conditions approaches the level at which it would itself cause an increase in blood sugar. There is no evidence that epinephrine from the adrenal glands is the factor which causes hyperglycemia when the function of insulin is interfered with. Hyperglycemia in the depancreatized dog is well marked after elimination of the adrenal medulla.

In considering the question of functions of the medulla it should be kept in mind that no important function can in any case be assigned to an organ the loss of which causes no symptoms. It is not so with the thyroid and the parathyroid glands, the islets and the adrenal cortex; their physiologic value is revealed by the consequences of their removal. They may, therefore, be assumed and are known to exercise important functions. It may seem curious that the adrenal medulla is abundantly supplied with nerves which control the output of epinephrine strictly, while it has not been proved that the production and discharge of the important hormones of the thyroid and parathyroid glands and islets are under the control of nerves. The adrenal cortex functions normally when the gland is denervated. If, as is currently believed, the adrenal medulla is composed of cells representing genetically sympathetic ganglion cells, it is to be expected that it should differ from

the other endocrine glands enumerated, for all of them are of quite different origin. The pituitary gland is left out of the discussion; little is known about its functions. Genetically, the anterior lobe would fit in with some of the other endocrine glands but not with the adrenal medulla.

We have suggested as a possibility that the reason for the close control of the output of epinephrine by the nervous system may not be to keep up the concentration in the arterial blood to a certain beneficial level, but to keep it below a certain harmful level. In the adrenal glands, there exists a stock of epinephrine which under abnormal conditions (for example, massage) can be liberated, not all at once, but so rapidly that harmful concentrations might be reached. This stock, amounting usually to about one-thousandth of the moist weight of the adrenal glands, possibly 1 per cent of the moist weight of the medulla, could easily be dangerous were it possible for it suddenly to escape into the adrenal veins.

It is impossible to go into the interesting observations, first put on a sound basis by Elliott, on the store of epinephrine. This, of course, represents a balance between production and discharge; its amount gives no direct information as to changes in the rate of output. Intense and prolonged emotional disturbance causes no effect on the store of epinephrine, but numerous drugs diminish it greatly.

THE PATHOGENESIS OF ASPIRATORY ABSCESS OF THE LUNG

ITS POSSIBLE RELATION TO ABSCESS OF THE LUNG FOLLOWING TONSILLECTOMY *

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Pulmonary suppuration following tonsillectomy occurs with sufficient frequency to arrest the attention of both the surgeon and the internist, but the exact method of its development is still in dispute. Aschner,[1] who studied the different types of pulmonary suppurative lesions encountered in the human being in the material obtained from resections of the lobe performed by Lilienthal, differentiated the following types: (1) bronchiectasis; (2) bronchiectatic abscess; (3) suppurative pneumonitis, and (4) extrabronchial abscess. Groups 3 and 4 frequently merge into each other, as areas of suppurative pneumonitis may break down and develop into a large extrabronchial abscess. It is the bronchiectatic abscess group which was of particular interest in the present investigation, as in each of the ten cases studied by Aschner this condition followed the operative removal of the tonsils and adenoids under general anesthesia. In one of the four cases of suppurative pneumonitis, the condition developed a few days after tonsillectomy; in the other three, as a sequence to pneumonia.

The clinical occurrence of postoperative abscess of the lung has been extensively reviewed by Cutler and Hunt [2] and by Schlueter and Weidlein.[3] It is surprising to note the exceedingly large number which has followed tonsillar operations. In a series of 1,908 cases of abscess of the lung reported by the Schlueter and Weidlein, 515, or 29.6 per cent, were postoperative, and of these tonsillectomy contributed 268,

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* Simultaneously with the submission of this article, a paper containing experimental evidence similar to that herewith reported was published by Minas Joannides (The Etiology of Pulmonary Abscess, *Surg. Gynec. Obst.*, October, 1928, vol. 47).

1. Aschner, P. W.: The Pathology of Lung Suppuration, Ann. Surg. **75**:321 (March) 1922.

2. Cutler, E. C., and Hunt, A. M.: Post-Operative Pulmonary Complications, Arch. Surg. **1**:114 (July) 1920; Post-Operative Pulmonary Complications, Arch. Int. Med. **29**:449 (April) 1922. Cutler, E. C.: The Etiology of Post-Operative Pulmonary Complications, S. Clin. N. Amer. **2**:935 (Aug.) 1922.

3. Schlueter, S. A., and Weidlein, I. F.: Post-Operative Lung Abscess, Arch. Surg. **14**:457 (Feb.) 1927.

or 14.6 per cent of the entire group. Of course, this group includes reports by authors who stressed tonsillectomy as the most frequent predisposing factor of postoperative abscess of the lung. On the other hand, Lyman,[4] who recorded 20,000 tonsillectomies performed under nitrous oxide anesthesia in the medical department of Washington University, did not report a single case of postoperative abscess of the lung. Hedblom[5] recorded only 2 of 20,000 at the Mayo Clinic. Moore,[6] publishing data of 450,000 tonsillectomies, obtained through questionnaires, reported abscesses in 202 cases, an average of 1 in every 2,500 to 3,000. Herb,[7] in a series of 12,045 operations on adenoids and tonsils, saw 2 abscesses of the lungs. Glowacki,[8] collecting data from various hospitals in St. Louis, found 1 in every 358 tonsillectomies, and Keiper[9] stated that 1 of 781 tonsillectomies was followed by abscess of the lung.

Obviously, such apparently conflicting statistics give rise to the questions: 1. How many of these cases were followed up after tonsillectomy? 2. What part does individual susceptibility to pulmonary infection play in its occurrence? 3. Is the presence of preoperative respiratory infections of importance? 4. What rôle, if any, does operative technic assume in the pathogenesis?

It is not within the province of this paper to enter into a discussion of all four questions. Some have already been covered by Myerson,[10] Wessler[11] and others. My task is rather to review the clinical observations briefly only as far as they may have a bearing on the pathogenesis of abscess following tonsillectomy; to sift the available data with reference to the two outstanding hypotheses, namely, the

4. Lyman, H. W.: Relation of Nose and Throat Operations to Lung Abscess, J. Missouri M. A. **20**:418 (Dec.) 1923.

5. Hedblom, C. A.: The Surgical Treatment of Acute Pulmonary Abscess, Illinois M. J. **47**:267 (April) 1925.

6. Moore, W. F.: Pulmonary Abscess: An Analysis of Two Hundred and Two Cases Following Operative Work About the Upper Respiratory Passages, J. A. M. A. **78**:1279 (April 29) 1922.

7. Herb, I. C.: Post-Operative Lung Complications, J. A. M. A. **79**:339 (July 29) 1922.

8. Glowacki, B. F.: Pulmonary Abscess: A Study of Ninety Cases, Laryngoscope **33**:153 (Feb.) 1923.

9. Keiper, G. F.: The Tonsil Question Up to Date, Laryngoscope **31**:777 (Oct.) 1921.

10. Myerson, M. C.: Pulmonary Aspects of Tonsillectomy Under General Anesthesia, Laryngoscope **32**:929 (Dec.) 1922; Lung Abscess Following Tonsillectomy: A Contribution to the Etiology, Arch. Otolaryng. **1**:137 (Feb.) 1925.

11. Wessler, H.: Lung Abscess and Bronchiectasis: A Clinical and Roentgenological Study of 100 Cases, Am. J. Roentgenol. **6**:161 (April) 1919; Suppuration and Gangrene of the Lung: A Study of 100 Cases, J. A. M. A. **73**:1918 (Dec. 27) 1919.

embolic and the aspiratory origin of abscesses following tonsillectomy, and finally to present experimental evidence which tends to corroborate the aspiratory theory.

In considering the pathogenesis of abscess of the lung following tonsillectomy, three methods of infection naturally suggest themselves: (1) by direct lymphatic extension from the operative area, (2) by way of the bronchi through aspiration and (3) by way of the blood stream in the form of septic emboli.

In the assumption of the lymphatic route as a means of transmission, Clendenning [12] laid a great deal of stress on the work of Grober [13] who tried by experimentation on animals to establish a connection between the lymphatics of the neck and those of the lung. The latter drew his conclusions from experiments performed on twenty-eight animals, dogs and rabbits, three of which were successful. The injection of coloring matter, such as Chinese ink, into the tonsils showed the connective tissue of the neck along the larynx to the aperture of the thorax colored symmetrically. "The lymphatic glands along the large blood vessels, as well as those in the supraclavicular region, were deeply stained. The coloring matter was found within the lymphatic vessels and in the paravascular spaces. A fibrous exudate was found in the apexes of both lungs, thus forming a bridge of inflammatory material from the parietal to the visceral pleura. The coloring matter was also present in the exudate. The glands of the mediastinum were stained on the left side, as were also the bronchial glands." On the basis of these experiments, Grober built the hypothesis "that tuberculous infection of the apex of the lung may take place via the deep lymphatic chain, the supraclavicular glands, thence to the parietal lymphatic vessels where an inflammatory exudate is thrown across the visceral pleura." The evidence presented, however, is insufficiently convincing and is not substantiated by the well known studies of W. S. Miller,[14] whose investigations do not in any way indicate a direct connection between the cervical lymphatics and those of the lung. Nor has Most [15] succeeded in demonstrating any

12. Clendenning, L.: The Cause of Abscess of the Lung After Tonsillectomy, J. A. M. A. **74**:941 (April 3) 1920; Abscess of Lung, Laryngoscope **32**:128 (Feb.) 1922.

13. Grober: Ballenger Diseases of the Nose, Throat and Ear, Philadelphia, Lea & Febiger, 1914, p. 398.

14. Miller, W. S.: Some Essential Points in the Anatomy of the Lung, Am. J. Roentgenol. **4**:269 (June) 1917; The Vascular Supply of the Pleura Pulmonalis, Am. J. Anat. **7**:389, 1908.

15. Most, A.: Die Topographie des Lymphgefaessapparates des menschlichen Koerpers in ihren Beziehungen zur den Infectionswegen der Tuberkulose, Bibliotheca Medica, part C, no. 21, Stuttgart; Untersuchungen ueber die Lymphbahnen an der oberen Thoraxapertur und am Brustkorb, Arch. f. Anat. u. Entwcklngsgesch. **30**:1, 1908.

communications between the lymphatics draining the tonsillar region and those draining the lung and mediastinum.

From a clinical point of view, the majority of opinion is in favor of the aspiration theory. Schlueter and Weidlein stated that in a census of recent contributions on the subject, forty declared themselves in favor of aspiration as the cause of abscess, while only ten favored embolism. The proponents of the embolic theory of the causation of abscess following tonsillectomy based their conclusions on the following facts: (1) the failure to produce abscess of the lung experimentally in dogs by endobronchial methods; (2) the relatively frequent development after local anesthesia; (3) the late development of symptoms; (4) the high incidence following other operations performed in potentially infected fields, and (5) the greater percentage of occurrence after procedure in mobile areas.

The reasons advanced for the aspiration theory are summarized as follows: (1) the common association with general anesthesia; (2) the clinical evidence that aspiration occurs; (3) the high incidence after tonsillectomy and other operations on the upper respiratory tract, and (4) the frequency of involvement of the lower lobe.[16]

The unsuccessful efforts of workers previous to 1926 to reproduce experimentally by aspiration pulmonary suppuration in dogs, together with the considerations enumerated, induced Cutler,[2] Schlueter,[3] Holman [17] and others to favor embolism rather than aspiration as the most important factor in the causation of postoperative suppuration of the lung. They argued that tonsillectomy is a common operative procedure, and yet the experimental production of abscess of the lung by aspiration is an impossibility. It must be noted, however, that their failure to produce abscesses in dogs by aspiration cannot be held as conclusive evidence that such a mechanism does not occur in human beings, especially in view of the innumerable clinical examples of pulmonary abscesses following the aspiration of foreign bodies. To this, however, I shall refer later.

In support of the embolic theory, these workers further adduced: (1) the clinical evidence of some observers who have collected a greater percentage of pulmonary complications in patients operated on under local anesthesia (these pulmonary complications, however, included embolic pneumonitis without suppuration); (2) experimental observations which support the view that so-called postoperative pneumonias

16. Wessler stated that, on the contrary, involvement of the upper lobe is more frequent.

17. Holman, E.; Weidlein, I. F., and Schlueter, S. A.: A Method for the Experimental Production of Lung Abscess, Proc. Soc. Exper. Biol. & Med. **23**:266, 1926.

are embolic in origin (Mason [18]), and (3) the occurrence of fatal postoperative embolism (Capelle [19]).

There seems to be no need for controversy as to the possible occurrence of postoperative pneumonia or abscess of the lung of embolic origin. Following the breaking off of a piece of infected material and its lodgment in the lung, infarction and necrosis of infected tissue may frequently occur.

The statement that just as many pulmonary complications arise after local anesthesia when the cough reflex is apparently not depressed seems, on the surface, to eliminate anesthesia as an important factor and to support the embolic theory. Such cases are reported by Porter,[20] Simpson and Noah [21] and Warthin,[22] while in 202 cases collected by Moore,[6] 39, or 19.3 per cent, of the operations were done under local anesthesia. The use of local anesthesia in these cases does not, however, warrant the assumption that the subsequent abscess of the lung was embolic in nature. Most interesting in this connection is the recent work of Ochsner and Nesbit [23] in which is shown the fallacy of the theory that local anesthesia, because it is limited to the pillars of the fauces, does not interfere with the protective mechanism of the respiratory tract. These authors said that in more than 600 cases of bronchography, performed according to the "passive" technic, aspiration into the tracheobronchial tree occurred following the anesthetization of the pharynx. In a series of five cases of tonsillectomy done under local anesthesia, Ochsner and Nesbit found that when iodized oil—40 per cent was administered to the patients with instructions to swallow it, it could be fluoroscopically demonstrated that the oil passed into the trachea and bronchi instead of into the esophagus. These observations led them to conclude that every patient on whom tonsillectomy is performed under local anesthesia, may aspirate some of the material which enters the pharynx during the time of the operation. They stated the belief that the development of an abscess is chiefly dependent

18. Mason, E. C.: Blood Coagulation: The Production and Prevention of Experimental Thrombosis and Pulmonary Embolism, Surg. Gynec. Obst. **39**:421 (Oct.) 1924.

19. Capelle, W.: Einiges zur Frage der postoperativen Thromboembolie, Beitr. z. klin. Chir. **119**:485, 1920.

20. Porter, W. B.: Pulmonary Abscess Following Tonsillectomy Under Local Anaesthesia, Virginia M. Monthly **47**:606 (March) 1921.

21. Simpson, J. R., and Noah, H. G.: Report of Two Cases of Lung Abscess Following Tonsillectomy Under Local Anaesthesia in Tubercular Subjects, Pennsylvania M. J. **23**:332 (March) 1920.

22. Warthin, A. S., quoted by Frank, I.: On Lung Abscess as a Sequel to Tonsillectomy, Laryngoscope **27**:474 (June) 1917.

23. Ochsner, A. J., and Nesbit, W.: Pulmonary Abscess, Arch. Otolaryng. **6**:330 (Oct.) 1927.

on the character of the aspirated material and on the retention of the protective cough reflex which Chevalier Jackson has aptly termed the "watch dog of the lung."

GENERAL EXPERIMENTS ON ASPIRATION

The extensive clinical evidence in favor of the aspiratory theory as a cause of abscess of the lung following tonsillectomy has led to a great deal of experimentation to substantiate this belief. As forerunners to the actual production of experimental abscess of the lung by this method, the concurrent studies by Lemon [24] and Hoelscher [25] on aspiration in dogs under general anesthesia are of special interest.

Lemon introduced various substances into the cheek of the dog's mouth by dripping them at a rate not much in excess of that at which saliva is produced. His experiments were conducted under ether anesthesia. An attempt was made both in the administration of the anesthetic and in the posture of the animal to simulate as nearly as possible the operative technic on human beings. He found that: (1) placing the subject on an inclined plane increases the risk of extensive aspiration of mucus from the mouth into the lower respiratory passages; (2) this is lessened as the plane passes through the horizontal to a decline, and vanishes when a Trendelenburg position is reached; (3) in all other postures the dogs aspirate into the lower passages or into the depth of the lungs, especially the lower lobes, regardless of whether the head is in a straight line with the body and muzzle up or whether the head is held to one side. The dangers are increased when light anesthesia is employed, when the animal struggles, breathes stertorously, swallows or vomits. The material used in these experiments apparently played no significant rôle, as various opaque substances in variable amounts were carried upward against gravity and into the trachea and bronchi. He also stated the belief that infection about the upper air passages is an important consideration in all operations requiring general anesthesia, for bacteria that had been placed in the mouth (*Bacillus prodigiosus*) as well as organisms the normal habitat of which is the mouth, were obtained from the lung tissue. He concluded from these experiments that postoperative pulmonary infection may be explained, in part at least, as a result of infection carried to the lung in oral secretions, which have been aspirated by the force of the air current created when the chest expands in persons whose protective mechanism has been disturbed.

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24. Lemon, W. S.: Aspiration: Experimental Study, Arch. Surg. **12**:187 (Jan.) 1926.

25. Hoelscher, R.: Experimentelle Untersuchungen ueber die Entstehung der Erkrankungen der Luftdege nach Aethernarkose, Arch. f. klin. Chir. **57**:175, 1898.

The work of Hoelscher on animals parallels that of Lenon. In corroboration of this experimental data, Myerson's [19] clinical observations are of great importance. He examined 100 patients bronchoscopically immediately following tonsillectomy performed under light anesthesia. Twenty-two retained the cough reflex; of these, 18 had no blood or mucus in the tracheobronchial tract and 4 did. Of the remaining 78 who did not cough during the operation, although they retained the laryngeal reflex, in only 6 was the tracheobronchial tract free from blood or mucus. According to Myerson, the preservation of the laryngeal reflex does not assure the occurrence of cough when the pharyngeal contents come into contact with the larynx, trachea or bronchus. The mixture of blood with mucus and saliva may not induce a sufficient stimulus to set up a cough reflex. On the other hand, anesthesia deep enough to abolish the cough reflex readily permits aspiration of mucus into the tracheobronchial tract.

UNSUCCESSFUL EXPERIMENTAL STUDIES IN ASPIRATION

The earliest attempts at the experimental production of abscess of of the lung by aspiration were made by Aschner.[1] In conjunction with his studies on the pathologic changes in abscess of the lung he investigated this question in dogs by insufflating intratracheally pieces of infected tonsils, adenoid tissue, pus from cases of abscess of the lung and cultures of anaerobes. All his results were negative. Lambert and Miller [26] introduced anaerobic bacteria intratracheally into monkeys without the production of abscess. Scarff [27] opened the chest of dogs and injected 1 cc. of semisolid agar containing virulent pneumococci into the center of a pulmonary lobe. Under fluoroscopic guidance, he also injected agar which contained virulent streptococci, staphylococci, sputum from clinical cases of abscesses of the lungs and organisms recovered from the nasal discharge and from the lungs of dogs that died from distemper. He stated that in all of the experiments he failed to produce chronic suppuration of the lung even when he injected enormous quantities and at frequent intervals. The preliminary injection of boiling water through the wall of the chest into the center of a lobe to produce necrosis and the occlusion of the bronchus with foreign bodies failed to cause a chronic infection in the lung even after organisms were introduced as previously described.

Schlueter and Weidlein,[3] in an attempt to produce pulmonary suppuration by aspiration, carried out a series of fifteen experiments on dogs (under ether anesthesia and morphia), employing the broncho-

26. Lambert, A. V. S., and Miller, J. A.: Abscess of the Lung, Arch. Surg. **8**:446 (Jan.) 1924.

27. Scarff, J. E.: Pulmonary Blood Pressures: An Experimental Study, Arch. Surg. **12**:591 (Feb.) 1926.

scope for the purpose of introducing various substances directly into the bronchi, but even by such methods none of the dogs developed any pulmonary lesions.

SUCCESSFUL EXPERIMENTAL PRODUCTION OF ABSCESS OF THE LUNG BY ASPIRATION

The previous failures to produce suppuration of the lung by aspiration led to the investigations by Kline,[28] Smith[29] and Allen,[30] who reported their results in 1927. Kline, employing material from dental caries and pyorrhea alveolaris containing spirochetes and fusiform bacilli, claimed to have produced pulmonary gangrene in rabbits by insufflation. Smith also reported the production of abscesses in mice, guinea-pigs and rabbits by the intratracheal inoculation of materials scraped from the alveolar border of the teeth of patients suffering from moderate severe pyorrhea. Thirty per cent of his animals remained well, 50 per cent died from pneumonia and 20 per cent developed pulmonary abscesses. Smears and cultures from these abscesses showed the same organisms as those used in the injection material. Although grossly the abscesses produced were connected with a bronchus, none was described as bronchiectatic. As a matter of fact, histologic studies of these lesions are not reported.

Smith's conclusions were that the aspiration of infected material from the teeth and tonsils in all probability accounted for the greater number of pulmonary abscesses, and that a small number might result from infected material aspirated from the upper respiratory tract.

Following the technic of Smith, Allen was unable to produce either abscesses of the lung or pneumonia. He attributed his negative results to the supposition that spirochetes found in the upper respiratory tract in normal persons, together with the cocci and fusiform bacilli present in the material used for injections, were killed by a fifteen minute exposure at room temperature. By altering his technic he succeeded in obtaining what he interpreted as abscess of the lung in three of fifteen dogs. His conclusions were that obstruction of the bronchus plays a dominant rôle in the formation of experimental aspiratory abscess of the lung, and he also ascribed the greatest significance to the development of the "multiple abscesses" in the dogs, because clinically most patients exhibit multiple lesions rather than a single abscess with cavity.

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28. Kline, B. S.: Experimental Gangrene, J. Infect. Dis. **32**:481 (June) 1923; Spirochaetal Pulmonary Gangrene, J. A. M. A. **77**:1874 (Dec. 10) 1921.

29. Smith, D. T.: Experimental Aspiratory Abscess, Arch. Surg. **14**:231 (Jan.) 1927.

30. Allen, D. S.: Etiology of Abscess of the Lung, Arch. Surg. **16**:179 (Jan.) 1928.

It seems to me, however, that the presence of single or multiple abscess is dependent on the number of widely separated foci simultaneously infected and followed by abscess formation. It is also probable that the multiple abscesses seen in human beings are due to the spread of the infectious material from bronchus to bronchus as a result of persistent coughing which is present in the earliest stage of the disease. This mode of dissemination is strikingly exemplified in acinous phthisis.

PERSONAL OBSERVATIONS

In the further elaboration of the aspiratory theory I carried on experiments in an effort to reproduce this condition in dogs. A series of twenty-seven dogs was employed in the investigation. These animals were first subjected to section of both recurrent laryngeal nerves. A period of several days was allowed to elapse in order to permit the healing of the preliminary operation. Sections of these nerves, as subsequently shown, had apparently no effect on the outcome of the experiments, as negative results were in the preponderance. The dogs were narcotized by the injection of iso-amyl-ethyl barbituric acid intraperitoneally in order to eliminate ether anesthesia as a factor in the production of pulmonary congestion.

The essential object in this study was to establish the fact that the aspiration of bacteria was responsible for the production of suppuration irrespective of any trauma of the upper respiratory tract. With this in mind, 0.5 cc. of twenty-four hour old broth culture of bacteria grown on Noguchi mediums, obtained from the sputum of patients suffering with abscess of the lung, was injected into the bronchus of the lower lobe of the lung of a dog by means of a bronchoscope. The twenty-four hour cultures contained spirochetes, fusiform bacilli, streptococci and staphylococci and were employed in most of the experiments. Before this cultured material was injected, from 1 to 2 drops of fresh, purulent sputum from the same patient from which the organisms had been obtained originally were added to make up the final 0.5 cc. used. Mixed cultures were used because most abscesses of the lungs contain a multiplicity of bacteria. Whenever single strains of organisms (streptococci) were employed, the dogs developed either pneumonia or nothing at all. Of 20 dogs injected via the bronchoscope, 2 (dogs 4 and 5) developed single encapsulated abscesses of the lower lobes, 1 (dog 467) several abscesses, two in the lower lobe and one in the upper lobe of the right lung; a fourth dog (dog 77) had a suppurative pneumonitis, and a fifth (dog 87) presented an involvement of the lower lobe characterized by a large scar within the lobe, which was adherent to the diaphragm. The appearance of this lesion was similar to the abscesses of the lower lobes which had been obtained in dogs 4 and 5, except that it looked healed. In this experiment the same cul-

tures were used as employed in dogs 4 and 5, with the exception that they were forty-eight hours old and probably less virulent. This may also have accounted for the rapid healing.

TECHNIC

The technic as employed by Dr. Sidney Yankauer and members of his staff who assisted in this work was as follows:

Dogs were employed in these experiments exclusively. They were first anesthetized with a 2 per cent solution of iso-amyl-ethyl barbituric acid, intraperitoneally. From 3 to 4 cc. of such solution, per kilogram of body weight, was administered to each dog, which induced sleep within fifteen minutes. A bronchoscope was introduced into the animal as far into the divisions of the main bronchi as possible; then a small cannula, 1.5 mm. in diameter, but long enough to reach well beyond the bronchoscope, was introduced and advanced as far into the bronchioles as it would reach. To this cannula a glass syringe was attached, by means of which 0.5 cm. of various bacterial mixtures were injected. The material used for injection consisted of 0.5 cc. of a mixed culture of bacteria, containing streptococci, staphylococci, fusiform bacilli and spirilli, grown on Noguchi mediums for twenty-four hours. This culture was derived from the sputum of a patient suffering from chronic abscess of the lungs.

PROTOCOLS

Experiment 1.—May 25, 1926: Dog 1, weighing 8 Kg., was given 20 cc. of a 2 per cent solution of iso-amyl-ethyl barbituric acid intraperitoneally. Following the injection the dog manifested a marked febrile reaction and died within four days. Autopsy showed pneumonia involving all the lobes. Microscopic section also showed an extensive hemorrhagic pneumonia.

Five-tenths cubic centimeter of the same culture as that used in dog 1, except that it was mixed with 0.5 cc. of blood removed from the femoral vein, was injected simultaneously into dog 2. Following this injection, the dog slept profoundly for twenty-four hours. Between May 25 and June 5, the temperature ranged between 101.4 and 103 F. A roentgenogram taken on May 30 showed a pneumonic infiltration in the lower lobe of the right lung. On June 5, the dog was killed. Autopsy revealed an organizing pneumonia. Microscopic section corroborated the process.

Dog 3, weighing 8.5 Kg., was given injections in the same manner as dog 2. He reacted with a temperature ranging between 101 and 103 F. A roentgenogram taken on May 30 showed a pneumonic involvement of the lower lobe of the right lung. On June 7 the animal was killed. On microscopic section, hemorrhagic pneumonitis and areas of productive pneumonia were observed.

Experiment 2.—May 28, 1926: Dog 4, weighing 8 Kg., was given 30 cc. of iso-amyl-ethyl barbituric acid intraperitoneally. Two days beforehand the recurrent laryngeal nerves were cut so as to prevent the dog from barking. Five-tenths cubic centimeter of mixed culture from a case of abscess of the lung, plus some fresh pus obtained from the same case, were mixed in a syringe and introduced into the bronchus by the technic previously described. On May 30, the temperature of the dog rose to 103 F. The dog coughed on the slightest exertion and was extremely sick and inactive. Physical examination showed an area of bronchial breathing over the lower lobe of the right lung. Roentgen examination showed an

infiltration in the lower lobe of the right lung in the region into which the mixture of bacteria and fresh pus had been introduced. On June 5, eleven days after injection, the dog was killed. Autopsy showed a swollen lower lobe of the right lung which was widely adherent to the diaphragm. Within this lobe a hard nodule, 4 cm. in diameter, was felt, which on section proved to be an encapsulated solitary abscess. The capsule was composed of thickened, fibrous connective tissue which merged with the adhesions to the diaphragm. It was impossible to trace any direct connection between the abscess and a bronchus. It seemed to have been completely walled off. Microscopic section showed a fairly large abscess with an extensive area of central necrosis, in which polymorphonuclear cells, mononuclears, red blood cells and various broken down cellular elements were scattered. The necrotic mass was surrounded by a zone of granulation tissue which in turn was enclosed by a fibrous capsule of connective tissue, sending prolongations into the enclosed granulation tissue. Outside the fibrous capsule the lung showed an extensive pneumonitis with sections of collapse induration. The pleura was extensively thickened (fig. 1).

Experiment 3.—May 28, 1926: Dog 5, weighing 8 Kg., was given 30 cc. of isoamyl-ethyl barbituric acid intraperitoneally (two days after section of the recurrent laryngeal nerves); twenty minutes later the dog was profoundly asleep. Five-tenths cubic centimeter of culture plus fresh pus from the same case as used in dog 4 was employed. This mixture was introduced into the bronchus of the lower lobe of the left lung, in the same way as in the other experiments. The following day the dog was still asleep and extremely sick. The temperature ranged between 102 and 103 F. in the afternoons for the next week. Cough began on the third day after inoculation. The dog was killed on June 8. A roentgenogram showed an infiltration in the lower lobe of the left lung. Autopsy showed an enlarged lower lobe, in the lower end of which there was a hard, nodular mass, from 3 to 4 cm. in diameter. Section showed a central area of necrosis, and the cavity surrounded by a tremendous mononuclear infiltration interspersed with fibroblasts, which arose from the surrounding fibrous capsule already formed beyond the necrotic area. Surrounding this capsule was an extensive hemorrhagic pneumonia.

Experiment 4.—June 19, 1926: Injections of 1 cc. of culture of mixed streptococci plus fresh pus were made into dogs 68, 69 and 71, after the dogs had first been subjected to section of the recurrent laryngeal nerve. All three dogs succumbed the following day with an extensive hemorrhagic pneumonia.

Experiment 5.—June 29, 1926: Mixed cultures, including fresh purulent material, were injected into dogs 84, 85, 86 and 87, the same technic being employed. Dog 84 was killed on July 15 and showed normal lungs. Dog 85 was killed on July 7 and showed normal lungs. Dog 86 was kept alive until September 29, at which time reinjections of mixed cultures were made; he was killed on October 15. Autopsy showed normal lungs. Dog 87 was killed on July 13. Autopsy showed a thickened lower lobe of the left lung with marked adhesions to the diaphragm. Microscopic section showed scarring and fibrosis of the lung, the scar tissue leading from the diaphragm into the superimposed lung. It was impossible to state whether or not I was dealing with a healed abscess of the lung. The general appearance was suggestive, as the section resembled areas seen in the dogs with actual abscess of the lung.

Experiment 6.—Sept. 13, 1926: Injections of mixed cultures from cases of pulmonary abscess were made into dogs 73, 75, 77 and 78 on the same day, by means of the same technic. There were no spirochetes in these cultures, only anaerobic and aerobic streptococci. Dog 73 died on September 14 with extensive

hemorrhagic pneumonitis. Dog 75 survived and was killed on October 14; normal lungs were found. Dog 77 was killed on September 24. Histologic section showed evidence of a chronic pneumonitis and foci of suppurative pneumonia. Dog 78 remained alive, and on September 28 reinjections of a mixed culture of purulent material were made. This injection, as in some of the other experiments, was followed by a rise in temperature, which gradually subsided. The dog remained

Fig. 1.—Extensively thickened pleura, below the abscess.

well. On October 13, injections were again made, with negative results On October 25, intrabronchial injections of 0.5 cc. of bile were made into the same animal, a control for other experiments in which mixed cultures of streptococci plus bile were used for injection. The bile was used with the idea of reducing local resistance. The dog was finally killed on November 18. Histologic sections showed foci of hemorrhagic pneumonia and areas of interstitial pneumonia crowded with histiocytes containing foreign particles.

Experiment 7.—Oct. 25, 1926: Injections of 0.75 cc. of mixed culture plus 0.2 cc. of diluted bile were made into dogs 254 and 255. These dogs developed pneumonia followed by complete recovery.

Five-tenths cubic centimeter of mixed culture plus 0.2 cc. of diluted bile were injected simultaneously into dog 253; he was killed on November 16. Autopsy showed extensive swelling of the lower and middle lobes of the right lung, which were glued together by an interlobar exudate. Microscopic section showed acute and chronic pneumonitis. In certain areas productive pneumonia was also found. Cultures yielded a pure strain of anaerobic streptococci.

Experiment 8.—Dec. 4, 1926: A culture of anaerobic streptococci, recovered from dog 253, plus 0.2 cc. of dilute bile, were injected into dogs 492, 493 and 494. Twenty-four hours later all three dogs were found dead. Autopsy showed extensive hemorrhagic pneumonia in each case.

Experiment 9.—Jan. 3, 1927: Five-tenths cubic centimeter of streptococcus culture removed from dog 253, was injected into dog 487. The dog was killed on January 12. Autopsy showed nothing abnormal in the lungs.

An injection of 0.5 cc. of mixed culture plus fresh sputum from a case of abscess of the lung was made into dog 489. The injection was followed by death on January 5 from pneumonia.

Experiment 10.—Feb. 19, 1927: An injection of 0.5 cc. of mixed culture plus fresh sputum was made into dogs 467 and 468. Dog 468 died from pneumonia. Dog 467 lived for seven days. After the injection he became ill and began to lose weight. On the sixth day he showed a marked dyspnea, cough and emaciation. He was killed on the seventh day. At autopsy a foul-smelling effusion was found in the right side of the chest. The left side of the chest contained no fluid. Examination of the lungs showed a large abscess in the lower lobe of the right lung, which had broken through into the pleura and was responsible for the foul effusion. A small abscess was also present in the upper lobe of the right lung. Microscopic examination of the lobe of the right lung showed two large abscesses, one next to the other, separated by a pneumonic area of consolidation. Each of the abscesses was surrounded by an extensive polymorphonuclear exudate, at the periphery of which was a fibrin net enmeshing polymorphonuclear cells and cocci. The necrotic central area of the abscess held numerous clumps of bacteria. The bronchi within this area were partly destroyed, their walls necrotic, the ciliated epithelium scattered and their lumina filled with a fibrinous exudate containing scattered polymorphonuclear cells in the center. The entire picture was that of a severe destruction of lung and bronchi (fig. 2).

SUMMARY OF PATHOLOGIC OBSERVATIONS

It is obviously impossible to compare the pathologic changes as described by Aschner in abscesses of the lungs in human beings, with those seen in the experimentally induced abscesses reported. On the one hand, in Aschner's material from human beings the pulmonary changes were of three or more years' duration. In the dogs the abscesses produced were characterized by a process of destruction which was rapidly followed by an attempt at repair. This was evidenced by the presence of a capsule of connective tissue about the abscesses in two of the dogs as early as the eleventh day. These abscesses were walled off and microscopically showed direct communication with the small bronchi.

A summary of the protocols showed that eight of the dogs that received injections recovered and remained well, thirteen succumbed to pneumonia, three developed pulmonary abscesses and one suppurative pneumonitis. Dog 87 probably showed the results of organizing pneumonitis. As determined by roentgenograms and confirmed by histo-

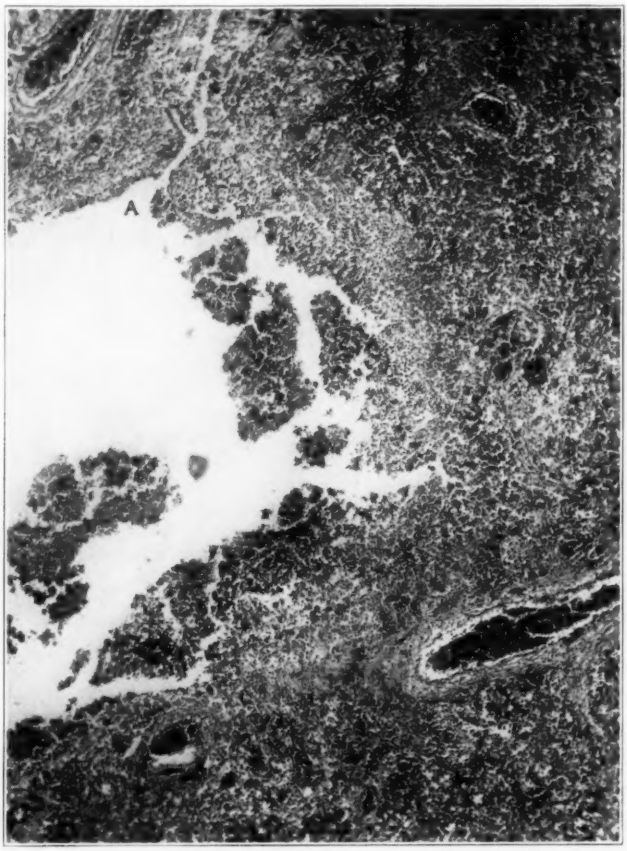

Fig. 2.—Destruction of the lung and bronchi; *A*, small bronchiole opening into the abscess cavity.

logic study, the abscesses appeared to develop as a primary diffuse pneumonitis with progressive diminution in the size of the pneumonic area until nothing but a small infiltration remained which, at autopsy, proved to be an abscess. Clinical as well as the experimental observations also attest to the fact that a pneumonic infiltration always precedes

the development of an abscess of the lung resulting from the aspiration of bacteria intrabronchially.

Histologic sections of the lungs of dogs 4 and 5, which were killed on the eleventh day of their illness, showed an abscess surrounded by extensive granulation tissue and fibrous bands which formed a well defined capsule. In dog 467, which died on the seventh day of the illness, there was a ruptured abscess in the upper lobe of the right lung. The lower lobe of the right lung was swollen, and histologically showed a large central area of necrosis. The larger bronchi within the necrotic tissue were filled with a fibrinopurulent exudate. The walls of the bronchi were necrotic, their mucosa denuded and the accompanying blood vessels thrombosed. Many of the smaller bronchi, alveolar passages and sacs were completely destroyed. The visceral pleura was greatly infiltrated and in parts thickened by granulation tissue.

Cultures from the abscesses of dogs 4 and 5 yielded streptococci which at first grew anaerobically only and subsequently aerobically, the spirochetes and fusiform bacilli having entirely disappeared. There was no fetor. The smears from dog 467 presented a mixture of streptococci and gram-positive bacilli but no spirochetes.[31] The disappearance of the sporochetes raises the question as to whether they were sufficiently viable before injection even though, microscopically, evidence of their motility was present, or whether the bactericidal properties of the lungs of the dogs were sufficiently strong to dispose of them. In Allen's dogs, with the exception of the one in which both the bronchus and the artery were ligated, a similar experience is recorded, seemingly pointing to the explanation that the lungs of the dogs are easily capable of disposing of these comparatively saprophytic organisms.

COMMENT

A survey of the literature on experimental abscess of the lung following tonsillectomy still presents two theories of the mode of formation, embolism and aspiration. The proponents of the embolic theory have produced experimental abscesses by introducing foreign bodies into the circulation with the production of an individual embolic abscess. These investigators claim that embolic abscesses are usually single, which is contrary to the general experience as seen at the autopsy table. It is only when a large vessel is occluded by a large embolus which does not readily break up that an extensive single area of necrosis follows. Even admitting the possibility of the occasional embolic origin of an abscess following tonsillectomy in human beings,

31. No cultures were made in this case because the autopsy was not done under sterile conditions.

it does not necessarily follow from the work of these investigators that all abscesses are to be explained on this etiologic basis. The occurrence of a single abscess is not an absolute criterion of their embolic nature. The results with intrabronchial insufflation of mixed cultures in the production of single abscesses refute such contentions.

It is significant from all the experimental work in this field that no one has been able to produce chronic abscess of the lung with the pathologic picture described by Aschner in human beings. The abscesses produced by means of emboli were designated by their authors as parenchymatous. Those induced by Smith were described as "walled off and in connection with a bronchus," but not bronchiectatic. Even the abscesses produced by Allen, which give the impression of being areas of suppurative pneumonitis rather than true abscesses of the lungs, were described as "remote from the main bronchus," the infectious material seeming to have been trapped in smaller bronchioles. There is nowhere mention of bronchiectatic abscess.

It is of significance that abscesses of the lungs have been reproduced in dogs, as well as in smaller animals, by aspiration without previous trauma to the respiratory tract, and that in the experiments no more than 0.5 cc. of mixed culture was necessary for this purpose. The probable factors in the successful experimental production of such abscess in the dogs in contrast to previous failures of some investigators are to be found in the imprisonment of bacteria in the bronchi as suggested in Allen's experiments, and possibly in the abolition of the cough reflex through the administration of iso-amyl-ethyl barbituric acid as an anesthetic which induced sleep for twenty-five hours. The sleep prevented expulsion of the infectious material and enabled the bacteria to multiply. The repeated presence of pneumonia, resulting in suppuration both in the dogs reported and in those of Allen, and the presence of single and multiple abscesses show that aspiration can be the causative factor of abscesses following tonsillectomy.

If the aspiration theory of abscess following tonsillectomy is examined from the point of view of its development, it is probably as follows: Aspiration of bacteria producing pneumonia constitutes the first stage. With the occurrence of the pneumonitis and cutting off of the active circulation, diminished local tissue resistance ensues. The rapid increase of bacteria, many of which are proteolytic,[32] together with the toxins and inflammatory by-products (enzymes, etc.) leads to the liquefaction of the tissue involved and the formation of abscesses. Other areas of the lungs may become infected by organisms introduced from the original necrotic area through coughing. Pneumonic areas

32. Many strains of streptococci cultivated on Noguchi mediums isolated from cases of abscess of the lung, which were employed in the experiments, showed definite proteolytic properties in vitro.

arise about these abscess cavities, which may serve as rich reservoirs for the maintenance of the numerous types of bacteria as well as of the spirochetes usually found. It is a well known fact that when spirochetes are not recovered in the sputum, they are invariably found in the edges of all abscess cavities and are in all probability secondary invaders. These pneumonic areas in their turn break down and lead to an extension of abscess formation. Simultaneously, however, as in all other inflammatory processes, destruction is associated with repair. In the process of destruction, the smaller bronchi involved in the abscess completely disappear, as seen in the sections presented, and the surrounding pulmonary tissue shows interstitial inflammation. This leads to the formation of connective tissue which later shrinks, drawing with it and stretching the partially destroyed and dilated, but more resistant, bronchi. Such a process with the consequent stenosis and kinking of remaining bronchi may in the course of events lead to actual bronchiectatic cavity formation. Should the process of destruction proceed more rapidly, the abscess becomes more extensive. In human beings, Aschner stated that, "About the abscess cavity the bronchial branch leading into it and the bronchus passing out of it, the lung tissue is converted into a firm, indurated mass showing dense bands of connective tissue separating grayish-yellow, raised areas. When the main lobe bronchus is the site of the abscess, the whole parenchyma shows the fibrotic lesion."

It is obvious from this description that the lung tissue, after several years of destruction and repair, becomes shrunken until practically a fibrous mass containing bronchiectatic cavities and a large bronchus belonging to the lobe is all that is left. The conception that the initial process may be a circumscribed bronchial lesion leading to stenosis and subsequent distal dilatation with the formation of a primary bronchiectatic cavity deserves consideration. Such a conception, however, seems to gain its origin from a study of the end-stages alone. The initial stages in abscesses in dogs, on the contrary, if these may be taken as criteria, in a study of lesions in human beings suggest the pneumonic origin. This is frequently also seen clinically. It is repeatedly confirmed by the roentgen rays and is associated with the expectoration of foul-smelling sputum containing spirochetes, fusiform bacilli, streptococci, etc. Such a pneumonic process, which may even go on to partial necrosis, may subside and completely heal within from three to six weeks in 30 per cent of cases (Wessler [11]). In the remaining cases, destruction of lung tissue proceeds. The persistent cough which disseminates the infectious material into contiguous bronchi with the usual sequence of events, i.e., bronchopneumonia, necrosis of pulmonary tissue and bronchial elements, fibrosis and dilatation of the remaining bronchi, completes the cycle which may finally end with the production of the bronchiectatic cavities.

CONCLUSIONS

1. A consideration of the pathogenesis of pulmonary suppuration following tonsillectomy has been presented from the points of view of the embolic and aspiratory hypotheses.

2. Results of experimentations on animals as well as clinical experience point to the fact that while embolic abscesses may occur, they are exceptional. The greater amount of evidence is in favor of aspiration as the mode of production of suppuration of the lung following operations on the upper respiratory tract.

3. Three of twenty-seven dogs that received, through the bronchoscope, 0.5 cc. of mixed cultures of bacteria recovered from the sputum of patients with abscesses of the lungs following tonsillectomy, developed abscesses with cavities, one developed pulmonary suppuration and a fifth presented evidence of a healed suppurative process in the lower lobe of the left lung—14.8 per cent of pulmonary suppuration.

4. Suppuration following tonsillectomy, characterized by Aschner as bronchiectatic, extrabronchial abscess and suppurative pneumonitis, have been found by him in specimens of the lungs studied from two to five years after tonsillectomy. While the last two forms have been obtained by me experimentally, bronchiectatic abscess could not be produced by this method in dogs. The reason suggested for this failure is to be found in the rapid tendency on the part of abscesses experimentally produced in dogs to go on to healing. Encapsulation of the abscess was already observed as early as the eleventh day.

5. The development of pulmonary abscesses in dogs is first manifested by the presence of pneumonia as demonstrable by the roentgen rays. This is comparable to the condition seen in the human being in the earliest stages following tonsillectomy. Subsequent stages of this condition, as studied histologically in the dogs, are characterized by the occurrence of necrosis within the pneumonic area and in cavity formation. This may persist or go on to healing.

6. If results obtained in dogs may be translated to the conditions occurring in man, it is suggested that following aspiration of infectious material from the upper respiratory tract, the current of events is as follows: (1) pneumonitis; (2) necrosis and cavity formation; (3) healing or persistence of the primary abscess with the formation of secondary bronchiectasis.

INSULIN IN ACROMEGALIC DIABETES*

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I recently reported a case of hyperpituitary disease with diabetes in which the efficacy of insulin was found to be impaired to a marked degree.[1] Nearly all other authors have claimed, however, that acromegalic diabetes does not differ from pancreatic diabetes in the patient's response to treatment with insulin. I referred to some of them (John,[2] Hetzel,[3] Sachs and MacDonald,[4] and Blum and Schwab[5]) and demonstrated that the evidence presented by them was inadequate to prove their claim.

Yater,[6] in an article published simultaneously with mine, again attempted to show that insulin is in every respect as effective in acromegalic diabetes as it is in the pancreatic type. He reported three cases and cited Colwell,[7] among others, in support of his contention.

It is my purpose here to show that a critical analysis of Yater's and Colwell's results and of the figures they publish does not yield such an interpretation. On the contrary, it is easily demonstrated that their results support the opposite contention. The apparent importance of these articles, Yater's written from the Mayo Clinic and Colwell's from Woodyatt's clinic, demands all the more a critical review.

It has been demonstrated by many experimenters, some of whom I quoted, that injections of pituitary extract exert an antagonistic action on insulin. This fact suggests that the diabetes of acromegaly may be the result of a similar antagonism exerted by excessive pituitary secretion on normally secreted endogenous insulin; this, in turn, leads to

* Submitted for publication, Nov. 14, 1928.
* From the Evans Memorial for Clinical Research and Preventive Medicine.

1. Ulrich, H.: The Antagonism Between Insulin and Pituitary Extract: Its Demonstration in a Patient with Acromegaly, Arch. Int. Med. **41**:875 (June) 1928.

2. John, H. J.: Spontaneous Disappearance of Diabetes, J. A. M. A. **85**: 1629 (Nov. 21) 1925.

3. Hetzel, K. S.: Glycosuria in Acromegaly, Lancet **1**:440 (Feb. 27) 1926.

4. Sachs, E., and MacDonald, M. E.: Studies in Experimental Pituitary and Hypothalamic Lesions, Arch. Neurol. & Psychiat. **13**:335 (March) 1925.

5. Blum, L., and Schwab, H.: Diabète acromégalique et insuline, Compt. rend. Soc. de biol. **89**:195 (June 8) 1923.

6. Yater, W. M.: Acromegaly and Diabetes, Arch. Int. Med. **41**:883 (June) 1928.

7. Colwell, A. R.: The Relation of the Hypophysis to Diabetes Mellitus, Medicine **6**:1, 1927.

the expectation that an additional supply of insulin, given by the parenteral route, will be partly or wholly ineffective. That was found to be true in the case that I reported.

The patient has died since the report was made. The antemortem diagnosis of pituitary neoplasm was confirmed at necropsy. A large pituitary adenoma was found.

During the course of his illness the patient had two attacks of pronounced glycosuria and hyperglycemia. The first extended over a period of about a month and then disappeared spontaneously; the second came on nearly two years later and continued until the time of death. Insulin appeared to have little effect on the level of the blood sugar during both of these periods, as is shown by the figures and charts contained in my previous article.

In the literature I have found only one other case (Mahler and Pasterny [8]) that was reported for the purpose of demonstrating the relative inactivity of insulin in acromegalic glycosuria. The patient had a proved pituitary tumor. Sixty units of insulin did not affect the hyperglycemia.

Another case of apparently the same type was reported by Falta.[9] Here the diagnosis was doubtful, although the glycosuria, low basal metabolic rate, obesity and extremely small sella turcica suggested a hypophyseal influence. The blood sugar, before treatment with insulin was begun, was 226 mg. per hundred cubic centimeters of blood. Insulin was given for a period of nine days, at first 90 units a day and later 140 and 150 units. The level of blood sugar remained high, varying during this time between 220 and 250 mg. per hundred cubic centimeters.

Yater [6] reported six cases of acromegaly with diabetes in three of which insulin was used. His contention that acromegalic diabetes yields as readily as the pancreatic type to treatment with insulin is based on the reports of these three cases.

Table 1 is a condensation of Yater's tables illustrating his case 3. It shows that a daily dosage of 50 units of insulin was begun when the patient's blood sugar amounted to 364 mg. per hundred cubic centimeters. Two days later it had come down to 250 mg., and a week later to 160 mg. It will be noted, however, that the amount of carbohydrate in the diet was greatly reduced on the day before treatment with insulin was started. The reduction of blood sugar may therefore have been caused by dietetic restriction. At any rate, it is impossible to say how much of it was effected by the dietetic change and how much by insulin. The lower portion of the table suggests that the diet had the greater

8. Mahler, P., and Pasterny, K.: Klinische Beobachtungen über Insulinwirkung beim Diabetes mellitus, Med. Klin. **20**:337 (May) 1924.

9. Falta, W.: Ueber einen insulinrefraktären Fall von Diabetes mellitus, Klin. Wchnschr. **3**:1315 (July) 1924.

influence and may alone have been responsible for the lowering of the amount of blood sugar. It is shown that after an interval of twelve days without any insulin, the amount given was 15 units, or less than a third of that given at first; yet the blood sugar came down to 130 mg.; that is to say, it was lower when 15 units of insulin were used than when 50 units were used. But here again the diet had been reduced still further, which, of itself, is sufficient to explain the additional drop in the amount of the blood sugar. It is unfortunate that estimations of blood sugar apparently were not made during the period when insulin was not given.

Another of Yater's cases (case 5) concerns a woman suffering from acromegaly, hyperthyroidism and diabetes. Her history before entrance to the hospital included reference to two attacks of diabetic coma.

TABLE 1.—*The Data in Yater's Case 3*

Date, 1926	Carbohydrate in Diet, Gm.	Dextrose in Urine, Gm.	Blood Sugar, Mg. per 100 Cc.	Insulin, Units per Day
1/ 8	190	79.22	334	..
1/ 9	190	135.7	...	..
1/10	196	145.6	...	..
1/11	170	119	...	..
1/12	102	69.78	...	..
1/13	100	20.41	364	50
1/14	101	3.87	...	50
1/15	99	6.41	250	50
1/16	101	0.95	...	50
1/21	102	....	...	50
1/22	100	....	160	50
1/24	100	....	...	..
2/ 3	110	....	...	..
2/ 4	73	....	...	15
2/ 7	100	....	...	15
2/ 9	54	....	...	15
2/11	54	....	130	15
2/12	54	....	...	15
2/17	54	....	147	15

Insulin was used during both of them. The patient recovered from the first attack after two days. Other details of this attack are lacking. During the second attack, she received 300 units of insulin within forty-eight hours. She awoke for half a day, but relapsed into coma. It was "decided that she had been revived from diabetic coma only to go into a state of hypoglycemic shock." Twenty grams of dextrose was administered intravenously, and the patient recovered.

After she came to the hospital, the urine contained occasional small quantities of sugar, the amount of blood sugar was relatively low, and the quantity of insulin used was small. The results, therefore, were not striking, but they indicate that insulin appeared to have little effect.

Later, a partial thyroidectomy was performed. Three fourths of the right lobe was removed. The patient died nine days after the operation.

Table 2 gives the facts regarding urinary dextrose, blood sugar and the dosage of insulin collected during the postoperative period. It will

be seen that increasing amounts of insulin, even to the huge dose of 215 units a day, did not prevent a simultaneous rise in the amount of blood sugar.

Yater is at a loss to "explain the inability of insulin to affect the blood sugar" during this period. He suggests the possibility that a thyroid crisis was responsible for it, but states that a "thyroid crisis is incompatible with the histologic picture" of the thyroid gland of this patient.

On the other hand, it is obvious that the figures in table 2 should not be used as evidence of the inactivity of insulin in hyperpituitary disease. They were obtained after an operation on the thyroid when the patient was about to die. These complications may have masked any effect exerted by the hypophysis. And it may be said also that all of the other observations in this case, even if they tend to support Yater's contention—which they do not—, should be barred, because the case is not one of uncomplicated pituitary disease. Hyperthyroidism

TABLE 2.—*Postoperative Data in Yater's Case 5*

Date, 1927	Dextrose in Urine, Gm.	Blood Sugar, Mg. per 100 Cc.	Insulin, Units per Day
8/13	13.5	392	20
8/14	49.7	...	30
8/15	87.0	350	30
8/16	84.3	400	90
8/17	124.6	400	80
8/18	58.9	426	135
8/19	64.5	454	215
8/20	27.3	500	160

has its own effects on metabolism. The present incomplete knowledge of the endocrine functions and particularly of their interrelations does not enable one to separate fully the metabolic effects of hyperthyroidism from those of a complicating dysfunction of the hypophysis. Yater sensed this when he wrote that "the patient may have been on the crest of a wave of hyperthyroidism at the time of the [attacks of] coma."

Yater's third case in which insulin was used (case 6 of his whole series) also was complicated by disease of the thyroid. Dietetic restriction reduced urinary sugar from a "moderate amount" to a trace, and the blood sugar from 206 to 165 mg. per hundred cubic centimeters. Ten units of insulin was then given twice a day to remove the traces of sugar from the urine, but it is not recorded how the blood sugar was affected by the insulin. This case is, therefore, without value in this connection. In the historical record of the patient, however, one reads that before he entered the hospital he "had often taken as much as 160 units in a day without severe reaction." It would appear, then, that the case could be cited with greater propriety as proof of the hampered action of insulin than as evidence of its efficiency.

Yater reached the conclusion that both the acromegalic and the pancreatic types of diabetes are the results of the same cause, namely, an insufficient production of insulin. Yet, he qualified this conclusion by saying that in acromegalic diabetes "it is possible that enough insulin might be secreted but might be neutralized by some new substance." To this I would add that such a new substance, as Borchardt [10] suggested long ago, is most likely to be an excessive pituitary secretion. If it might neutralize the normally secreted endogenous insulin, it might just as readily neutralize some or all of any additional insulin injected under the skin.

In addition to his own cases, Yater referred to Colwell's paper [7] for support of his thesis. Colwell's article is a splendid review of the literature concerning the relation of the hypophysis to carbohydrate metabolism. The question of the efficacy of insulin in the diabetes of

TABLE 3.—*The Data in Colwell's Case*

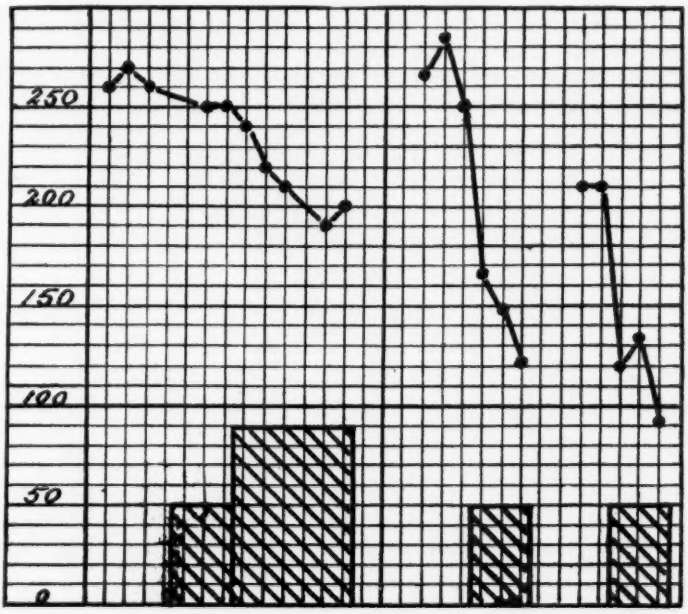
Date, 1925	Dextrose in Urine, Gm.	Fasting Blood Sugar, Mg. per 100 Cc.	Insulin, Units per Day
3/19	37.8	260	..
3/20	33.5	270	..
3/21	46.6	260	..
3/22	35.6	...	..
3/23	17.0	...	50
3/24	20.2	250	50
3/25	16.1	250	50
3/26	15.3	240	90
3/27	14.4	220	90
3/28	10.9	210	90
3/29	2.3	...	90
3/30	5.7	190	90
3/31	2.1	200	90

acromegaly is included. Colwell cited four cases from the literature and added one of his own to prove that insulin affects the diabetes of acromegaly "in a manner similar to that observed in ordinary diabetes mellitus."

Table 3 gives the essential data of Colwell's case. The diet remained constant throughout the period covered by the table. Fifty units of insulin a day, which is not a small dose, effected a reduction of the amount of blood sugar from 260 to 250 mg. per hundred cubic centimeters. This is practically negligible. Ninety units a day, which is a large amount, brought the amount of blood sugar down to 200 mg. I cannot agree with Colwell that these results show that insulin has acted "in a manner similar to that observed in ordinary diabetes mellitus." On the contrary, the same amounts of insulin given to patients with uncomplicated pancreatic diabetes will elicit a much greater response.

10. Borchardt, L.: Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, Ztschr. f. klin. Med. **66**:332, 1908.

This fact is shown in the accompanying chart. The curve at the left of the chart illustrates the effect of insulin in Colwell's case; the curves on the right were obtained with patients suffering from pancreatic diabetes. In all of the cases the level of fasting blood sugar had been stabilized by diet before insulin was used. The relatively minor variations in the first case of pancreatic diabetes do not contradict this statement; on the contrary, they emphasize the fact that a drop of the level of blood sugar amounting to only 10 mg. per hundred cubic centimeters, which Colwell credited to insulin, is not necessarily to be



Comparison of the effects on the fasting level of glycemia produced by insulin in Colwell's case (represented by the first curve at the left of the chart) and in two cases of pancreatic diabetes (represented by the second and third curves). The hatched areas represent the amounts of insulin given in each case. The scale indicates the number of units of insulin given each day and the number of milligrams of blood sugar per hundred cubic centimeters of blood.

regarded in that light. Colwell's case varied by that amount before treatment with insulin was begun.

Fifty units of insulin a day elicited a far greater response in the patients with pancreatic diabetes than it did in Colwell's case of acromegalic diabetes. In fact, this amount was more effective in these patients than was the larger amount of 90 units in Colwell's case. Both

patients with pancreatic diabetes suffered from fairly severe insulin shock on the evening preceding the last test for blood sugar included on the chart; both received orange juice at that time. Had this been omitted, the last amount of blood sugar recorded in each case would probably have been still lower. It was neither advisable nor necessary, therefore, to carry the comparison with Colwell's case further by giving 90 units of insulin as he had done. It is evident that the difference between the curves would stand out still more strikingly, had the portion representing the effect of 90 units in Colwell's case been omitted.

Colwell's case, therefore, adds further proof that insulin is less active in cases of acromegalic diabetes. The fact that a slight reduction of blood and urinary sugar in this form of diabetes may be effected by insulin is not sufficient evidence of its adequate action; its action must be shown to be as great as it is in the average case of pancreatic diabetes. It is likely that cases of acromegaly may respond in varying degrees to treatment with insulin. The variability may depend on varying intensities of hyperpituitary activity or, possibly, on other complicating influences.

Three of the four cases cited by Colwell from the literature, those of Sachs and MacDonald,[4] John,[2] and Blum and Schwab,[5] were discussed briefly in my previous article. They are taken up again in this paper, together with Hetzel's case,[3] which was not mentioned by Colwell.

Hetzel came to the conclusion that in his case "the glycosuria was identical with that of diabetes; it reacted similarly to insulin and control of the diet." This conclusion, however, does not agree with the text of the report of his case. There he stated that "insulin was increased successively to 40, 45, 50 and 60 units a day to lower this hyperglycemia [0.24 per cent]; but the effect was only small, for the blood sugar fluctuated throughout the day between 0.15 per cent and 0.20 per cent." In the history of the patient appears the statement that ten months before admission, he had been treated for his glycosuria by dieting. "Insulin was also tried, but it was said to have been without effect, and the efficacy of insulin was doubtful." All evidences of diabetes finally vanished, and it may have been this fact that brought Hetzel to the foregoing conclusion. If that is so, he was misled in that he misinterpreted a spontaneous recession of pituitary glycosuria, a common occurrence, as a therapeutic effect of insulin.

The fourth case cited by Colwell was reported by Etienne and his associates.[11] They gave "pancreatic extract (presumably insulin)" to a patient with acromegaly and glycosuria and observed that the glycosuria was reduced. Colwell, however, seems to have overlooked the

11. Etienne, G.; Drouet, L., and Yovannovitch-Brintcheva, B.: Glycosurie dans l'acromégalie, Rev. méd. de l'est **50**:271 (May) 1922. Etienne, G.: Sur la pathogénie de la glycosurie chez un acromégalique, Rev. neurol. **38**:730 (June) 1922.

important statement made by the French writers that a certain amount of sugar persisted and was not affected either by the continuous action of the pancreatic extract or by increasing the dose. They believed that part of the glycosuria was pancreatic in origin and therefore amenable to treatment with insulin, and that the irreducible residue was the effect of hyperactivity of the posterior lobe of the hypophysis and for that reason was not affected by insulin. In short, they concluded that true hypophyseal diabetes could not be influenced by treatment with insulin.

Aside from this point, however, their case is open to the objections that the amount of pancreatic extract given was not stated, nor is there any record of estimations of blood sugar. Furthermore, the case was not one of uncomplicated acromegaly, but, according to the authors, presented, in addition, hypertrophy of the thyroid, hypertrophy and noninvolution of the thymus, hyperactivity of the suprarenals and ovarian insufficiency.

The case of Sachs and MacDonald [4] is that of a woman operated on for "acute acromegaly." The operation was followed by glycosuria which, they stated, "in no way differed from the glycosuria of a diabetic patient," and which "was furthermore controlled by the administration of insulin." Glycosuria was apparently not present before the operation, so that it must be regarded as a result of operative trauma rather than as a symptom of pituitary disease. This places the case in a different category and does not prove the efficacy of insulin in true hyperpituitary glycosuria.

John's report of a case [2] concerns a man with acromegaly and diabetes. The blood sugar amounted to 440 mg. per hundred cubic centimeters at the time of his admission to the hospital. The patient was put on a restricted diet and received 100 units of insulin a day for ten days. The blood sugar had then reached the normal level. Insulin was reduced to 20 units a day and given in this amount for about two weeks. The amount of blood sugar remained normal. Insulin was then omitted, and the daily ration of carbohydrate was raised from 100 to 120 Gm. Protein and fat, also, were increased. Despite these changes "the patient kept a normal blood sugar level until he was discharged."

John concluded that the patient was cured of diabetes as a result of the treatment. He reported the case primarily for that purpose, together with another one, with diabetes of a lesser degree, in which insulin was not used but in which the loss of carbohydrate tolerance later vanished. It is noteworthy that both were cases of acromegaly. Cures of patients with true pancreatic diabetes are exceedingly rare; the spontaneous disappearance of acromegalic diabetes is relatively common. This must lead to the conclusion that John's cases were of the latter type. It is probable that the initial dietetic restriction in his

first case lowered the amount of blood sugar to some extent and may even have been the impetus that led to the eventual restitution of carbohydrate tolerance. In this sense it may be spoken of, perhaps, as a cure; but I believe that the tendency to spontaneous recession of glycosuria, shown in many cases of acromegaly, was the important determining influence in both of John's cases.

As far as the effect of insulin in his first case is concerned, definite conclusions cannot be reached. Curtailment of diet and treatment with insulin were started at the same time; hence, as in Yater's case, their separate effects cannot be estimated. The fact that blood sugar did not increase when insulin was omitted supports the argument that it was ineffective.

Blum and Schwab,[5] also quoted by Colwell, gave 30 units of insulin to each of two patients, one with acromegalic glycosuria, the other with pancreatic diabetes. The responses were essentially equal. Details about the patient with acromegaly are lacking. This is unfortunate. The reader is deprived of the opportunity of making an independent interpretation of the observations in the case. If, for instance, the previously quoted writers, Sachs and MacDonald, had failed to state that their patient had developed glycosuria after an operation, but had merely reported their case as one of acromegalic glycosuria amenable to insulin, the conclusions to be drawn from it would have been decidedly different. Nevertheless, in the absence of other evidence, the case of Blum and Schwab must be accepted as being presumably one of hyperpituitary loss of carbohydrate tolerance in which insulin was effective.

It may be, therefore, that there are gradations of antagonism against insulin in different patients with acromegaly, varying from none at all, as in the case reported by Blum and Schwab, to almost complete inhibition, as in the case which I have described. Several explanations of this variability suggest themselves. It may be brought about by varying intensities of hyperpituitary activity. "Or, if it is true that pituitary tumors may give rise to glycosuria by pressure on neighboring brain centers, the simultaneous presence of such a pressure type, which may be amenable to insulin, with a hypersecretory type, would lead to varying degrees of responsiveness to treatment with insulin. Again, it is conceivable that some of the patients may develop true pancreatic diabetes, owing to exhaustion of the pancreas from constant stimulation by the pituitary hyperglycemia. Such patients may then become more susceptible to treatment with insulin."

Yater stated that "the balance of evidence at hand from a clinical standpoint certainly favors the deduction that insulin acts in acromegalic diabetes just as it does in diabetes without acromegaly." I have attempted to show that critical analysis of this evidence, including his own, fails to support such a statement. On the contrary, most of the

evidence at hand favors the deduction that insulin acts less efficiently in cases of acromegalic diabetes than it does in diabetes without acromegaly.

The evidence, I believe, is sufficiently convincing to warrant the use of insulin for diagnostic purposes in cases of glycosuria that are suspected of having a hypophyseal foundation. A demonstrable failure of insulin to produce its expected and usual results should be regarded as a link in the chain of evidence leading to a diagnosis of hyperpituitary disease.

CLINICAL TYPES OF EDEMA IN THE HEART FAILURE OF CHILDHOOD*

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A study of the clinical course of edema in nephritis, recently published by Aldrich,[1] prompted me to attempt a similar study of the edema associated with heart disease in children. The underlying thought in both these observations has not been to advance any new theories regarding the cause and nature of edema, but rather to add precise clinical data to the knowledge of this interesting problem.

During the past five years, I have had the opportunity of observing a large number of children with heart disease, and as these children have gone on to recovery, chronic invalidism or death, I have been impressed with the wide variations in the symptoms and signs encountered. The clinical picture of associated edema in the child with heart failure, however, has always been one of two definite types, each one running a constant course, differing only in degree.

The first type of edema is the commonly recognized dependent type, involving the dependent portions of the body almost exclusively. It appears most prominently in the lower extremities, about the sacrum, and occasionally, depending on the position of the patient, in other portions of the body. With this type of edema there are usually found ascites, marked enlargement of the liver and other evidence of cardiac failure. As a rule, these children not only suffer from their discomfort and cardiac embarrassment, but are acutely ill and frequently toxic.

The second type of edema is generalized, and I have come to term it the "nephritic type," because of the similarity of the distribution to that seen in nephritis. It appears first in the face and later becomes equally prominent in all portions of the body. In degree it is never so overwhelming as that seen in nephrosis, but it has the same generalized distribution regardless of the position of the patient. Otherwise, the clinical picture is that of a patient with heart failure, though the heart failure is seldom so severe as that found in the previous type, nor is the patient ever so acutely ill. He appears more as a convalescent patient who has outlived an acute infection and presents the usually associated pallor and poor nutrition. The urinary observations are negative with

* Submitted for publication, Nov. 15, 1928.

* From the Cardiac Department of the Children's Memorial Hospital.

* Read at the Society of Internal Medicine, Chicago, March 26, 1928.

1. Aldrich, C. A.: A Study of the Clinical Course of Generalized Edema, J. A. M. A. **84**:481 (Feb. 14) 1925.

the exception of small amounts of albumin which are encountered no more frequently in the one type than in the other.

Little has been said about the second or generalized type of edema as seen in heart failure in children. Resnick and Keefer [2] recently commented and theorized about an edema of the face associated with myocardial insufficiency. Other mention of facial edema has been made by Cohen,[3] Mackenzie,[4] Miller [5] and Crummer;[6] however, their rather casual comments do not suggest the idea that this is a true clinical entity appearing in the heart failure of childhood. This is the more remarkable since generalized edema in the child with cardiac disease is not of exceedingly rare occurrence in a large service of children with heart disease.

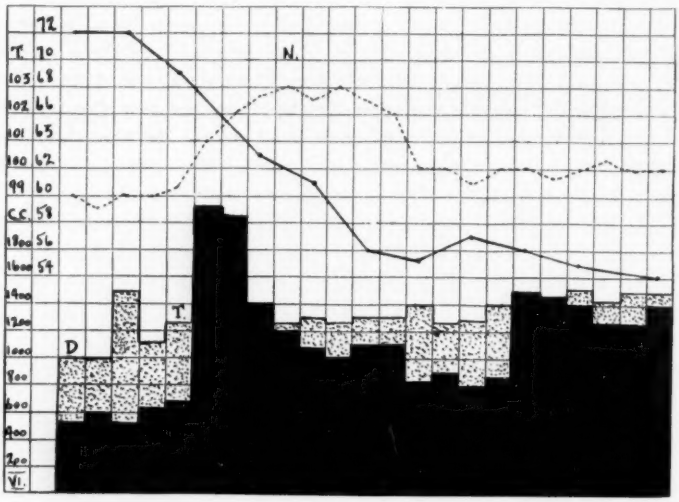

Chart 1.—Generalized edema. Digitalis (*D*) did not give results. Elimination occurred following the administration of theobromine sodio-salicylate (*T*). A marked rise in temperature and nausea (*N*) were observed.

I have not been able to associate the type of edema with any definite lesion of the heart, as it has appeared during the course of most of the

2. Resnik, William H., and Keefer, Chester S.: The Significance of Edema of the Face in Myocardial Insufficiency, J. A. M. A. **85**:1553 (Nov. 14) 1925.

3. Cohen, Milton B.: Edema in Myocardial Insufficiency, Correspondence, J. A. M. A. **85**:1829 (Dec. 5) 1925.

4. Mackenzie, James: Diseases of the Heart, ed. 3, London, Oxford University Press, 1918, p. 307.

5. Miller, R.: The Medical Diseases of Children, Bristol, John Wright & Sons, 1911, p. 374.

6. Crummer, Leroy: Clinical Features of Heart Disease, New York, Paul B. Hoeber, 1925, p. 24.

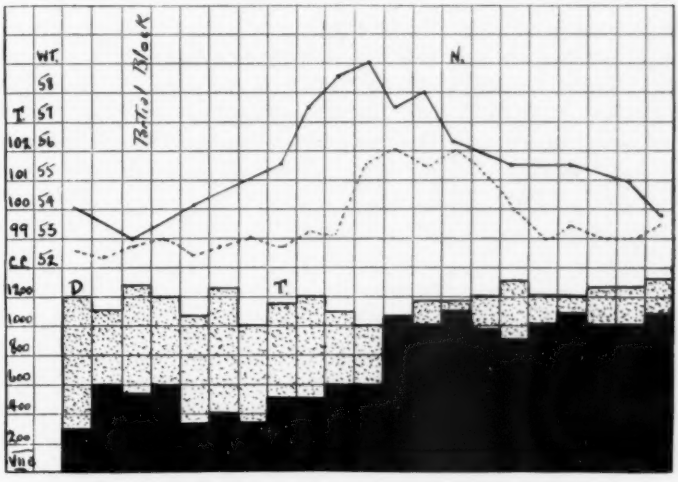

Chart 2.—Generalized edema. In spite of digitalis (*D*) carried to the point of block, elimination did not occur. Following the administration of theobromine sodio-salicylate (*T*) diuresis together with a rise in temperature and toxic symptoms (*N*) appeared.

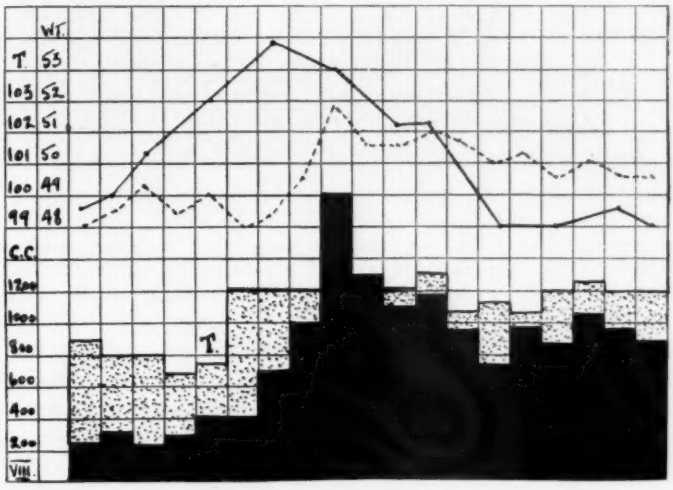

Chart 3.—Generalized edema. Theobromine sodio-salicylate (*T*) produced elimination with a rise in temperature.

clinical types commonly encountered in childhood. There appears, however, to be some definite relationship between generalized type of edema and the recentness of the infectious invasion of the heart. In other words, when the reserve of the chronically diseased heart has been encroached on and failure ensues, a dependent type of edema usually is produced, while in the recently invaded heart, in which one feels there is still active infection, a generalized edema is more likely to occur. In either case, infection is an important factor, for I am convinced that cardiac failure in childhood is generally infectious in origin, though the active process may frequently be extracardiac. It may be possible

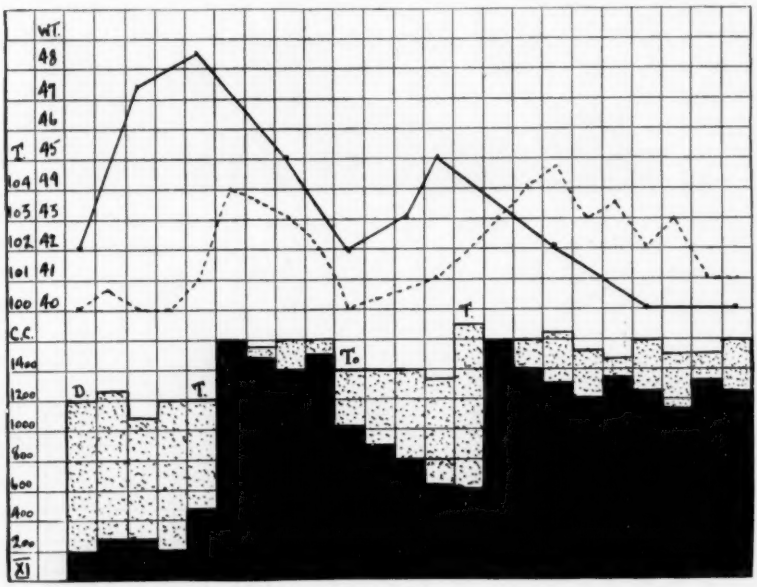

Chart 4.—Generalized edema. There was no response with digitalis (*D*). Theobromine sodio-salicylate (*T*) produced elimination with a rise in temperature; when omitted (*To*) edema and weight increased. Elimination was reestablished with theobromine sodio-salicylate (*T*) with toxic symptoms and a rise in temperature.

at some later date, after further observations have been made, to formulate a more definite relationship between the type of lesion of the heart and the type of edema revealed. For the present, my observations lead me to think that it depends rather on the stage of the cardiac involvement, as to whether the infectious process is acute or chronic.

Further convincing evidence that two definite types of edema occur in heart failure in children is presented by the clinical courses of these

attacks. It was noted that in the generalized type, following the improvement of the condition of the heart, together with the reabsorption of the edema fluid, increased elimination and subsequent loss of weight, and toxic symptoms occurred. For the most part these were mild, consisting of headache, nausea and a rise in temperature. On two occasions they were moderately severe. It was thought at first that these symptoms were possibly due to the therapeutic measures resorted to in attempting to reestablish the heart and prompt elimination. This

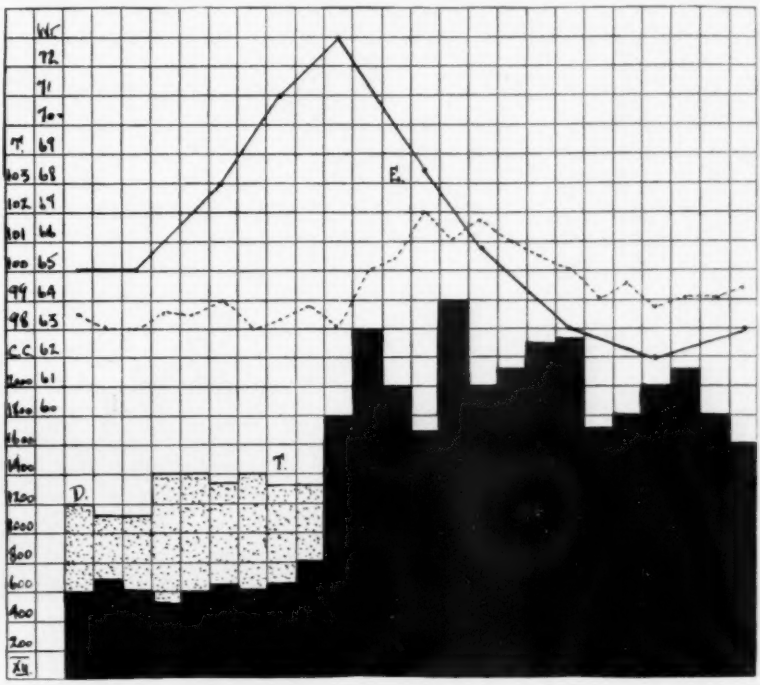

Chart 5.—Generalized edema. The administration of digitalis (*D*) after a long period did not give results. Following the use of theobromine sodio-salicylate (*T*) elimination was established. A rise in temperature, toxic symptoms and emesis (*E*) followed.

possibility has been disproved by the observation that many other patients underwent the same treatment with equally large doses of the drugs employed and showed neither toxic symptoms nor a rise in temperature. The marked elevation of temperature during and following elimination is a convincing observation and is easily demonstrated from charts (charts 1, 2, 3, 4 and 5). If the temperature had been

normal during the edematous stage, a rise was noted with elimination. If the temperature had previously been elevated, it rose higher during diuresis. This toxic phase of the clinical course was a constant observation in the patients with generalized edema, while in those with the dependent type of edema it never occurred (charts 6, 7, 8, 9, 10, 11 and 12).

Furthermore, it was also found that each type responded to different therapeutic measures. Digitalis was, of course, used in most of the cases. In some of the patients seen recently it was used up to the point of digitalization. This was done, not because of definite cardiac

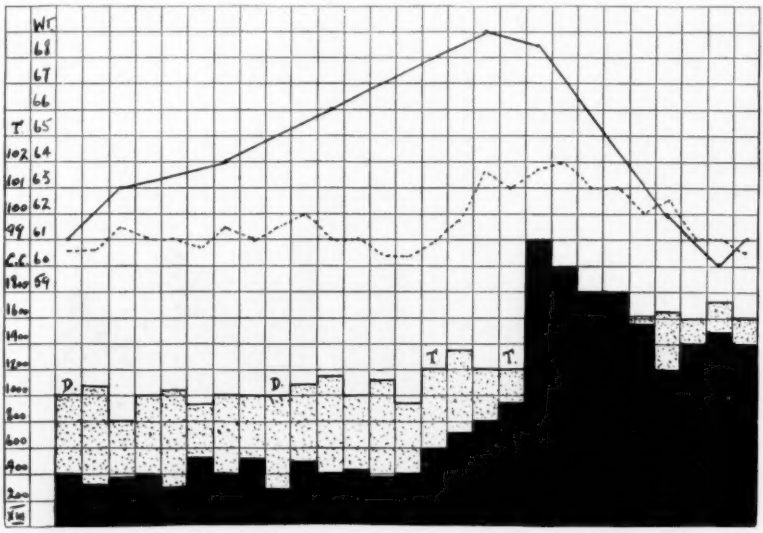

Chart 6.—Generalized edema. Repeated use of digitalis (*D*) did not cause elimination. A prompt response occurred with the administration of theobromine sodio-salicylate (*T*). A rise in temperature appeared also.

need, but rather for control purposes to convince myself that digitalis alone was not always the necessary measure to produce diuresis.

It was demonstrated that in the dependent type of edema the use of digitalis was frequently sufficient to cause diuresis and that the addition of the simple diuretics did not hasten or even alter the course. If their combined use had no effect, abdominal paracentesis and merbaphen or organic mercury compound had to be used. Elimination alone, however, in these cases does not appear ever permanently to improve the condition. The mercurial diuretics have given splendid results, but in children the temporary lessening of the cardiac burden as a result

of the enormous elimination produced is rarely sufficient to assist in recovery. I am of the opinion that the reason for this is that the cause of the cardiac failure, infection, is not eliminated, and therefore the process again repeats itself.

In the generalized type of edema digitalis, regardless of the amount prescribed, did not shorten the clinical course of the condition. Theobromine sodio-salicylate, however, acted almost as a specific. Results were obtainable in many of the patients with a generalized type of edema with theobromine sodio-salicylate alone, digitalis not being indicated. This therapeutic response has been so constant that it is now almost a matter of routine, in the ward for patients with cardiac disease, to use theobromine sodio-salicylate in the generalized type of cardiac edemas, while in the dependent type efforts are confined entirely to the

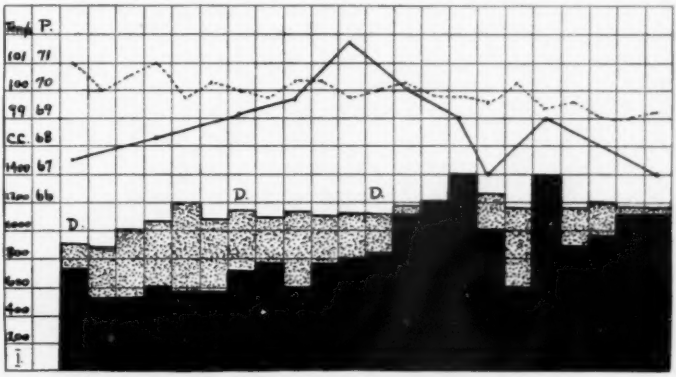

Chart 7.—Cardiac edema. The patient responded to increasing doses of digitalis (*D*). Neither toxic symptoms nor a rise in temperature occurred.

use of digitalis; if no response is noted, the stronger mercurial diuretics are eventually resorted to.

From a prognostic standpoint, the determination of the type of edema present has also been of value. My observations have impressed me with the fact that edema of the dependent type carries with it a grave prognosis. Of the cases reported, five of six patients died. This, of course, is not attributed to the edema per se, but rather to the underlying condition of the heart which, as has been mentioned, is usually chronic.

In the children with generalized edema the immediate prognosis is good. Of the cases reported, only three of ten patients have since died. Ultimately, other cardiac breaks may come with a recurrence of edema of either type, but in the second or even the third attacks of generalized edema the prognosis continues to be better than in the dependent type.

These patients readily respond to treatment and, in spite of the toxic symptoms during the elimination period, their recovery is usually prompt. Other signs of failure, however, may continue after the disappearance of the edema, but these respond to the usual forms of treatment.

COMMENT

The observation that edema associated with heart failure may be generalized is not entirely new. That it does occur in children, however, as a distinct entity, without a demonstrable pathologic disturbance of the kidneys, responding almost specifically to treatment, producing a definite symptom-complex during diuresis and affording points of prog-

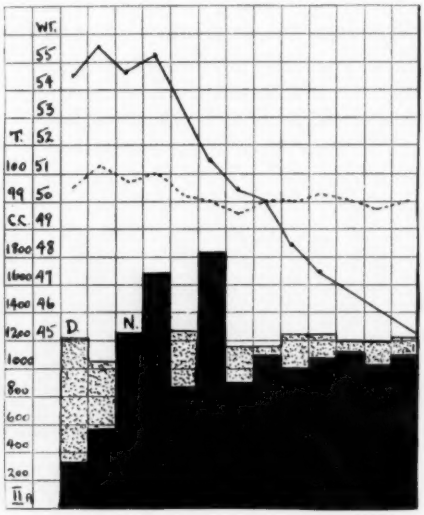

Chart 8.—Cardiac edema. There was no response to digitalis (*D*) until merbaphen (*N*) was used. Marked elimination and loss of weight resulted without toxic symptoms.

nostic import, has not been previously emphasized. The fact that aside from the commonly recognized dependent type of edema there does occur also this generalized type in the heart failure of childhood, and that each follows a separate and constant course, justifies the conclusion that different factors are at work in each. I do not presume to attempt to explain the mechanism involved, but certain hypotheses present themselves.

In the cases reported, actual lesions of the kidneys can be excluded. Though varying amounts of albumin were present in many of the patients, this observation occurred as frequently in one group as in the other. Casts were not found regularly in any case. Likewise, the

chemical examinations of the blood in neither group showed enough variation to warrant deductions. There were five patients in whom the nonprotein nitrogen was above normal, two of whom had purely dependent edema, while the other three were among those presenting the generalized type. Twice the uric acid was high, but here again the cases were divided equally between the two groups. In all other respects, the chemical readings on the blood were normal.

That edema of the purely dependent type is primarily mechanical in origin no one can deny. It is sometimes puncturable in these children; yet the intradermal salt solution test of McClure and Aldrich,[7] as demonstrated by Olmsted,[8] in children with cardiac disease shows a decreased absorption time in the lower extremities, indicating some

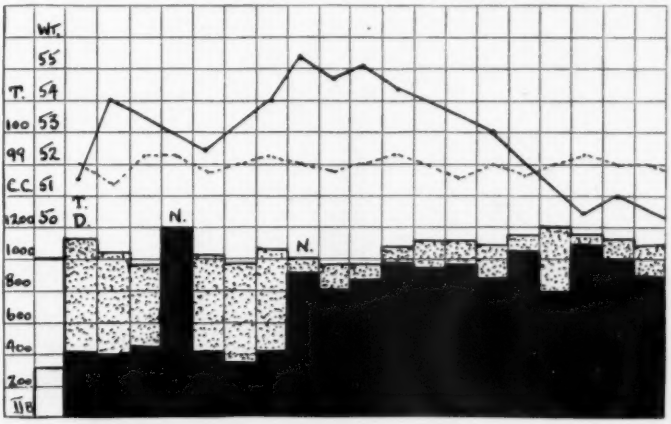

Chart 9.—Cardiac edema. There was no response to digitalis (*D*) or theobromine sodio-salicylate (*T*). After two injections of merbaphen (*N*) elimination continued without toxic results.

affinity of the tissues for water. In these conditions the sequence of stasis may occur with subsequent or coincidental change causing an increased demand for water on the part of the tissues, as suggested by Marriott [9] and Fischer.[10]

7. Aldrich, C. A., and McClure, William: The Intradermal Salt Solution Test, J. A. M. A. **82**:1425 (May 3) 1924.

8. Olmsted, H. C.: Intradermal Salt Solution Test in Cardiac Disease in Children, Arch. Int. Med. **37**:281 (Feb.) 1926.

9. Marriott, W. M.: Intoxications Associated with Alterations in the Physio-Chemical Equilibria of the Body Cells and Fluids, Tr. Am. Pediat. Soc. **35**:205, 1923.

10. Fischer, M. H.: Oedema and Nephritis, ed. 3, New York, John Wiley & Sons, 1921, p. 233.

In the cases of generalized edema it does not seem probable that stasis is an important factor. This assumption is based on the fact that the edema is generalized. Because of the generalized character it seems logical to conclude that the cause of the edema may be largely toxic. The peculiar clinical course of generalized edema during reabsorption and elimination, which shows toxic symptoms and a rise in temperature, may be of significance. If edema is a protective mechanism at times, or, in other words, an attempt by the body to dilute toxins, as suggested by Aldrich,[1] the withdrawal of the diluent might concentrate the hypothetic toxins and account for the symptoms

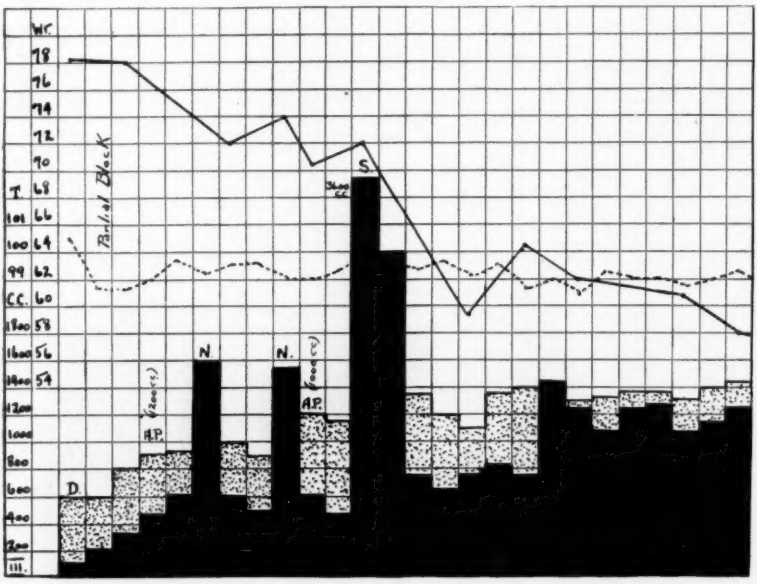

Chart 10.—Cardiac edema. Digitalis to the point of heart block did not produce results. Abdominal paracentesis (*A.P.*) followed by the administration of merbaphen (*N*) and an organic mercury compound (*S*) established elimination which continued without toxic symptoms.

encountered here. This sequence of events has so frequently repeated itself during these observations that the hypothesis seems likely. If generalized edema is a phase of the recently, and probably still actively, infected heart, it is suggested that this type of edema is not alone produced by impaired circulation, but primarily by the toxins resulting from the infectious process.

This contention is further substantiated by the results obtained in the case of generalized edema with the intradermal salt solution test of McClure and Aldrich.[7] In the generalized type the absorption time was

about equal in both the leg and the arm. The time for the leg was a trifle faster, but never by any great margin. In dependent edema there was a difference of from twenty to thirty or more seconds, with the rapid reabsorption always in the leg. Since this test indicates the affinity of the tissues for water, the results would suggest that in generalized edema this affinity is present to an almost equal degree throughout the body. Such a condition of affairs must be explained on a toxic basis. Vaquez [11] and others describes symptoms of a toxic nature following the reabsorption of edema, but did not mention the

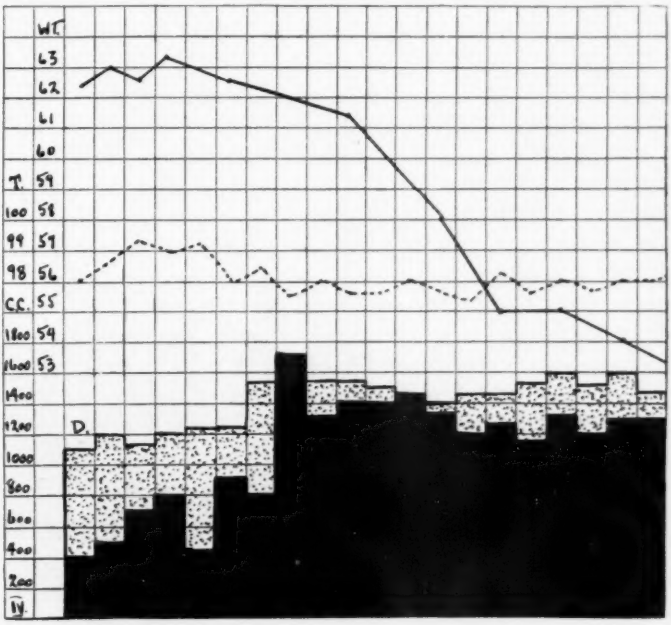

Chart 11.—Cardiac edema. Digitalis (*D*) alone produced elimination.

type of edema involved. Vaquez concluded that these symptoms must be contributed to a "sort of conflict within the economy between the organic media and the substances contained in the edematous fluid. . . ."

Whatever may be the correct answer to these purely theoretical queries, the fact still remains that in children with heart failure these two types of edema occur, which can be considered definite clinical

11. Vaquez, Henri: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1924, p. 651.

entities. Also it is true that the recognition of these clinical types of edema is of clinical significance and importance. The therapeutic measures to be instituted are almost specific, depending on the type of edema present, and a correct observation considerably hastens the convalescence of the patient. Likewise, the aid to prognosis is of value. In the cases herein mentioned, dependent edema associated with heart failure in children has always been of serious moment, and only one of the patients has responded permanently to treatment. There have been many others with dependent edema whose course terminated in death before sufficient diuresis occurred so that comparative charts could not be compiled for this study. The prognosis of generalized

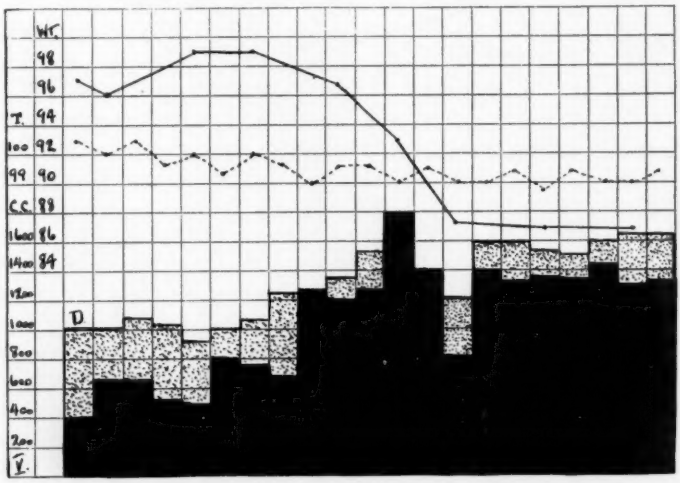

Chart 12.—Cardiac edema. Digitalis (*D*) alone produced elimination.

edema is always encouraging, provided there has not been pericardial involvement, which in itself affords, perhaps, the most serious complication in the heart of a child.

SUMMARY

1. Edema in the child with cardiac disease manifests itself in two types: the dependent or cardiac type and the generalized or "nephritic" type.

2. Response to treatment has shown a certain specificity which is of clinical value. (*a*) In the dependent type of edema digitalis is of value, while the addition of the milder diuretics aids little in hastening reabsorption and elimination. If digitalis fails, then the stronger mercurial diuretics are necessary. (*b*) In the generalized type of edema,

theobromine sodio-salicylate acts almost as a specific and usually without the aid of digitalis.

3. In the generalized type, there is a definite clinical picture produced during diuresis which is characterized by toxic symptoms such as headache, nausea and a rise in temperature. In the dependent type of edema these symptoms never occur during diuresis.

4. The type of lesion of the heart seems to influence little the kind of edema produced. It appears, however, that in the children whose history of heart failure is of recent date and whose hearts are, perhaps, still acutely infected, the edema associated with failure is more likely to be generalized. Dependent edema occurs almost exclusively in the patients with more chronic heart disease.

5. The prognosis for the patient with generalized edema is good, at least as to the immediate future, while that of the patient with the dependent type of edema is relatively bad.

6. It is suggested by the clinical observations of two types of edema seen in heart failure in childhood that different factors are at work in each. A few hypotheses have been discussed.

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PATHOLOGIC CHANGES IN AURICULAR FIBRILLATION AND IN ALLIED ARRHYTHMIAS*

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From time to time during the past twenty years studies have been made to determine the existence of a specific lesion in auricular fibrillation, auricular flutter and paroxysmal tachycardia. The experiments of Mines and of Garrey demonstrated the possibility of a circus wave of contraction in animal tissues, and those of Lewis showed definitely that circus movement is the mechanism of auricular fibrillation and flutter and possibly of paroxysmal tachycardia. Previous to the time of these experiments, pathologists were prone to consider lesions in or around the sino-auricular and auriculoventricular nodes as of great importance in these arrhythmias, and especially in auricular fibrillation. Recently, little in the way of microscopic study has been done in this field, but the consensus of opinion seems to be that there is no specific pathologic picture. From the standpoint of the new physiology, no visible organic disease is necessary, and the facts that auricular fibrillation and flutter may be paroxysmal and that the former may often be converted to normal sinus rhythm, no matter what the etiologic factor may be, by means of drugs which could not possibly alter structural disability are strong proofs for the nonexistence of a specific organic causative lesion. The present study has been made as an attempt to settle definitely, by microscopic methods, the question of a specific anatomic basis for these arrhythmias.

REVIEW OF LITERATURE

Most of the investigations of this problem were reported during the years from 1909 to 1915. Schönberg,[1] in 1909, carefully examined eleven hearts with perpetual arrhythmia, and Hedinger,[2] in 1910, added nine cases to these. All of these hearts showed changes in the regions of the mouths of the venae cavae and especially in the vicinity of Wenckebach's bundle. These changes consisted of lymphocytic collections, increase in fibrous connective tissue, or even atrophy and disappearance of the muscle fibers, with connective tissue replacement. In the nerves and ganglions lymphocytic collections or cellular masses con-

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* Work done in the Division of Medicine and the Section on Pathologic Anatomy as a Fellow in The Mayo Foundation, Rochester, Minn.

1. Schönberg, S.: Ueber Veränderungen im Sinusgebiet des Herzens bei chronischer Arrhythmie, Frankfurt. Ztschr. f. Path. **2**:153, 1909.

2. Hedinger, Ernst: Ueber Herzbefunde bei Arrhythmia perpetua, Frankfurt. Ztschr. f. Path. **5**:296, 1910.

sisting of spindle cells and lymphocytes often occurred. The auriculoventricular node was not usually involved. In other hearts without the arrhythmia, these changes usually were not found. Hedinger concluded that auricular fibrillation was probably due to lesions in the region of Wenckebach's bundle and the inferior vena cava.

In 1910, Koch[3] studied three hearts in which fibrillation had occurred. He also found inflammatory changes in the region of the orifices of the venae cavae in all and involvement of the nerves and ganglions in two. There were some changes in the sino-auricular node in all three. In one case, marked interstitial edema in this region and swelling of the muscle fibers were noted. Koch did not come to any definite conclusion regarding the cause of auricular fibrillation from this study, but in a later work he remarked that it is less the inflammatory infiltration of the sino-auricular node than the transcendency of a new center of auricular impulse and exhaustion of the normal center by overextension which is most important.

Draper,[4] in 1911, and Cohn,[5] in 1911, each reported the study of a case of auricular fibrillation in which there were severe pathologic changes in the sino-auricular node and other alterations elsewhere in the heart, but without marked lesions of the conduction system. In Cohn's case there was interstitial myocarditis, especially in the right auricle.

Freund,[6] in 1912, found changes such as sclerosis and lymphocytic infiltration in the sino-auricular node in three of five cases of auricular fibrillation. In four of the cases sclerosis of the auriculoventricular bundle occurred, and lymphocytic infiltration in two. In the fifth case there were no changes. Freund assumed that the irregular ventricular activity was due to impairment of conduction through a diseased auriculoventricular bundle, and that the only difference between heart block and auricular fibrillation was the failure of auricular activity in the latter.

Falconer and Dean,[7] in 1911, and Cohn and Lewis,[8] in 1912, each reported a case which showed sufficient destruction of the bundle of His

3. Koch, Walter: Zur pathologischen Anatomie der Rhythmusstörungen des Herzens, Berl. klin. Wchnschr. **1**:1108, 1910.

4. Draper, G.: Pulsus Irregularis Perpetuus with Fibrosis of the Sinus Node, Heart **3**:13, 1911.

5. Cohn, A. E.: A Case of Bradycardia with Post-Mortem Examination, Heart **3**:23, 1911.

6. Freund, H. A.: Klinische und pathologisch-anatomische Untersuchungen über Arhythmia perpetua, Deutsches Arch. f. klin. Med. **106**:1, 1912.

7. Falconer, A. W., and Dean, George: Observations on a Case of Heart Block Associated with Intermittent Attacks of Auricular Fibrillation, Heart **3**: 247, 1911.

8. Cohn, A. E., and Lewis, Thomas: Auricular Fibrillation and Complete Heart Block; A Description of a Case of Adams-Stokes' Syndrome, including the Post-Mortem Examination, Heart **4**:15, 1912.

to account for the chronic heart block which had existed. In the first case there also had been attacks of auricular fibrillation, and in the latter this arrhythmia had developed. There was no change in the sino-auricular node in the one, but marked sclerosis of the node in the other. There was, however, an increase of fibrous tissue in the right auricle in both instances. A similar case of Angyán,[9] in 1913, with complete auriculoventricular dissociation and subsequent development of auricular fibrillation showed complete division of the bundle of His by fibrous and fatty tissue and severe sclerosis of the sino-auricular node. Falconer and Dean,[10] in 1912, reported another case in which chronic auricular fibrillation had been complicated by occasional attacks of incomplete heart block. In addition to various valvular and muscular lesions there was extensive fibrosis and cellular infiltration of the auriculoventricular node and bundle and cellular infiltration of the sino-auricular node.

In 1912, Price and Mackenzie [11] reported a case of diphtheria with auriculoventricular dissociation and auricular fibrillation in which there was extreme degeneration and cellular infiltration of the cardiac muscle but no changes in the sino-auricular node or conduction system. Hume,[12] in 1913, studied a case of diphtheria with auricular fibrillation and found the sino-auricular node infiltrated with numerous mononuclear cells of the "formative type" and the specific fibers undergoing granular degeneration.

In 1913, Berger [13] reported a study of three cases of auricular fibrillation. In one the sino-auricular node was completely destroyed, and in the other two the specific system was not affected. He considered the fibrillation in the first case due to destruction of the node and in the other two, to dilatation of the right auricle.

Cohn,[14] in 1913, in a study of three cases of auricular fibrillation in horses, found the sino-auricular node and conduction system intact in all.

In 1913, Cohn and Heard [15] found changes in the specific nodes and the bundle of His in one case of auricular fibrillation but doubted any direct connection between the anatomic and clinical observations.

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9. Angyán: Kammerautomatie und Vorhoflimmern, Virchows Arch. f. path. Anat. **213**:170, 1913.

10. Falconer, A. W., and Dean, George: Observations on a Case of Auricular Fibrillation with Slow Ventricular Action, Heart **4**:87, 1912.

11. Price, F. W., and Mackenzie, Ivy: Auricular Fibrillation and Heart Block in Diphtheria, Heart **3**:233, 1911-1912.

12. Hume, W. E.: A Polygraphic Study of Four Cases of Diphtheria, Heart **5**:25, 1913.

13. Berger: Anatomische Untersuchungen des Herzens bei Pulsus irregularis perpetuus, Deutsches Arch. f. klin. Med. **112**:287, 1913.

14. Cohn, A. E.: The Post-mortem Examination of Horses' Hearts from Cases of Auricular Fibrillation, Heart **4**:221, 1913.

15. Cohn, A. E., and Heard, J. D.: A Case of Auricular Fibrillation, with a Postmortem Examination, Arch. Int. Med. **11**:630 (June) 1913.

Sutherland and Coombs,[16] in 1913, in a case of acute rheumatic carditis, discovered the sino-auricular node to be more strongly attacked by focal rheumatic myocarditis than the surrounding auricular muscle, and the conduction system showed diffuse infiltration.

In 1914, Romeis [17] reported three cases of auricular fibrillation in which severe sclerosis of the sino-auricular node was shown, but the auriculoventricular conduction system was intact in two.

In 1914, Jarisch [18] reported eight cases of auricular fibrillation in only two of which the sino-auricular node was intact. In all of the others there were moderate or severe changes in this node, and in all but two there were lesions in the conduction system. Jarisch concluded that there is, however, no specific pathologic condition in auricular fibrillation. He considered that the arrhythmia was a result of exhaustion of the sino-auricular node, incoordination between the activity of the sino-auricular and auriculoventricular nodes, the disturbing influence of impulse formation in other places and the supremacy of vagus influence when the activity of the sino-auricular node is depressed.

Hochhaus and Dreesen,[19] in 1915, found increase in connective tissue and cellular infiltration of the sino-auricular node in a case of auricular fibrillation, but Thorel,[20] in 1915, could not find pathologic changes in the right auricle or the specific nodes in a heart that he examined.

Wilkinson and Butterfield,[21] in 1915, in a case of paroxysmal heart block and auricular fibrillation, noted collections of small lymphocytes and vascular changes in the auriculoventricular node and bundle and an increase in fibrous tissue in the right auricle, but no lesions in the sino-auricular node.

In 1922, Fløystrup [22] studied nine cases of auricular fibrillation and six control cases with special reference to the microscopic changes in the sino-auricular node, the auricles and the nerves and ganglions near the node. In a few of the cases of auricular fibrillation, he found both fatty

16. Sutherland, G. A., and Coombs, C. F.: A Case of Acute Rheumatic Carditis and Auricular Fibrillation in a Child, Heart **5**:15, 1913.

17. Romeis, B.: Beiträge zur Arhythmia perpetua, Deutsches Arch. f. klin. Med. **114**:580, 1914.

18. Jarisch, Adolf: Zur pathologischen Anatomie des Pulsus irregularis perpetuus, Deutsches Arch. f. klin. Med. **115**:331, 1914.

19. Hochhaus and Dreesen: Vorkommen und Bedeutung von anatomischen Veränderungen des Herzmuskels bei Herzschwäche, Festschr. d. Akad. f. prakt. med. zu Cöln, 1915, p. 384.

20. Thorel, C.: Pathologie der Kreislauforgane des Menschen: I. Anatomie des Herzens, Ergebn. d. allg. Path. u. path. Anat. **17**:90, 1915.

21. Wilkinson, K. D., and Butterfield, H. G.: Paroxysmal Heart Block with Paroxysmal Auricular Fibrillation, Heart **6**:3, 1915-1917.

22. Fløystrup, G.: Studies on the Pathogenesis of Auricular Fibrillation, Acta med. Scandinav. **56**:12, 1922.

infiltration and fibrosis of the sino-auricular node; in one there was lymphocytic infiltration of the node; in a few, only some fatty infiltration of the node. The control cases usually showed similar conditions. After reviewing these cases, together with nineteen from the literature, he concluded that the cause of auricular fibrillation is not to be found in alterations in the sino-auricular node, in changes in the auricular myocardium, in dilatation of the auricles or in anatomic changes in the nerves. He argued that since quinidine caused cessation of the arrhythmia by its depressant effect on muscular activity, the fibrillation might be due to overexcitability of the auricular myocardium due to its working against an absolutely or relatively increased resistance. He believed that nervous influences might be of greatest importance in cases of paroxysmal fibrillation.

Mönckeberg,[23] in 1924, after reviewing the literature on the microscopic researches in auricular fibrillation, concluded that the arrhythmia is not dependent on disease of the sino-auricular node or on phenomena of interference between this node and the auriculoventricular node. He believed that the activity of the sino-auricular node not only is not depressed in auricular fibrillation but takes part even in the production of the stimuli leading to the fibrillation. To him Lewis'[24] explanation of the arrhythmia precluded the necessity of anatomic changes either in the specific system or in the myocardium.

In 1925, Frothingham[25] examined the auricles in eleven cases of acute and chronic auricular fibrillation and in twenty-three cases in which death occurred from acute or chronic disease but in which the heart action was regular. He did not find a gross lesion to be constant or essential, nor did he find definite or specific microscopic lesions in the sino-auricular node in cases of auricular fibrillation. He called attention to a certain appearance of the auricular muscle fibers in nine of the eleven cases of auricular fibrillation, and in four of the fifteen controls, which he was unable to decide had any significance for the fibrillation. Throughout the auricles there was edema of the muscle fibers with vacuolization and slight changes in the staining reaction suggestive of degeneration in these cases. In the more advanced form the vacuolization increased, the striations in the fibers disappeared in part and the changes in staining reaction were more marked. The nuclei of the fibers showed little if any change, and the disturbance in the fiber did

23. Mönckeberg, J. G.: Herz, in Henke, F. and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, vol. 2, Berlin, Julius Springer, 1924, p. 512.

24. Lewis, Thomas: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, Shaw & Sons, 1925.

25. Frothingham, C.: The Auricles in Cases of Auricular Fibrillation, Arch. Int. Med. **36**:437 (Sept.) 1925.

not necessarily extend over its length. There was little if any cellular reaction in the supportive connective tissue framework. Marked interstitial edema sometimes occurred, but it also was found in the control cases at times.

In 1928, Condorelli [26] reported an unusual case of auricular fibrillation with nodal rhythm of a frequency of 97. Extensive and highly inflammatory lesions of the subepicardial nerve plexus of the right auricle were present without other important lesions elsewhere in the heart tissue.

The literature contains the reports of only a few cases of auricular flutter in which a careful study of the heart was made. Ritchie,[27] in 1914, in a review of cases of auricular flutter, recorded the results in six necropsies: In one, the auriculoventricular bundle was fibrous. In another, there was acute pericarditis implicating the sino-auricular node and the abundant nerve elements in its vicinity. One heart showed diffuse interfascicular fibrosis in the thin, dilated right auricle and slight lymphocytic infiltration in some parts of the conduction bundle. The specific system was normal in a fourth heart, and there was slight fibrosis of the muscle. A case of diphtheria presented fatty degeneration of auricles and ventricles and pronounced interstitial myocarditis of the ventricles; the auriculoventricular node and bundle were healthy. Another case of diphtheria showed infiltration of the sino-auricular node with mononuclear cells of "formative type" and engorged capillaries and hemorrhages; the muscle fibers of the node were in a state of granular degeneration. Sutherland,[28] in 1914, and Neuhof,[29] in 1915, each reported a case without any specific changes.

The literature on studies of cases of paroxysmal tachycardia is also meager. Vaquez,[30] in 1909, and Cade and Rebattu,[31] in 1911, each recorded a case with changes in the bundle of His, and Falconer and Duncan,[32] in 1912, a case of "syphilitic myocarditis" with endarteritis, in which the sino-auricular node and conduction system were affected.

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26. Condorelli, Luigi: Sull'importanza delle lesioni infiammatorie del plesso sottoepicardico dell'orecchietta destra nella patogenesi di alcune turbe del ritimo cardiaco, Riforma med. **44**:613, 1928.

27. Ritchie, W. T.: Auricular Flutter, New York, Paul B. Hoeber, 1914.

28. Sutherland, G. A.: Auricular Flutter in Acute Rheumatic Carditis, Proc. Roy. Soc. Med. **7**:133, 1914.

29. Neuhof, Selian: Auricular Flutter Accompanying Acute Endopericarditis, M. Rec. **88**:995, 1915.

30. Vaquez, H.: Pathogénie de la tachycardie paroxystique, Arch. d. mal. du coeur. **2**:609, 1909.

31. Cade, A., and Rebattu, J.: Tachycardie paroxystique et lésions du faisceau de His, Bull. et mém. Soc. méd. d. hôp. de Paris **31**:476, 1911.

32. Falconer, A. W., and Duncan, G. M.: Observations on a Case of Paroxysmal Tachycardia of Auricular Type, Heart **3**:133, 1912.

A case reported by Falconer and Dean, in 1912, revealed rheumatic nodules with infiltration of the membranous septum and middle third of the crus communis in a case of this arrhythmia. In 1914, Butterfield and Hunt [33] reported a case in which there were changes in the wall of the auricle and sino-auricular node. Mönckeberg concluded that these changes were not consistent enough to account for the arrhythmia, since analogous observations have been made in the specific muscle system without clinical evidence of either a shunting out of the sino-auricular node or an increased automatic activity of the auriculoventricular node, which the observations in these cases were supposed to indicate.

ANALYSIS OF CASES

A series of 145 cases of auricular fibrillation, seven cases of auricular flutter and two cases of paroxysmal tachycardia, all with necropsies, was studied. The cases included practically all of the patients with these arrhythmias on whom necropsies were performed at The Mayo Clinic within the last few years; they were not a selected group. One begins to realize that the subject of cardiac disease cannot be discussed apart from the clinical course, because so few specific lesions are demonstrated. This entire series was investigated, therefore, to determine the clinicopathologic basis of the arrhythmia, and from the three groups of arrhythmias, hearts were selected for microscopic study with reference to their classification on such a basis. In all but a few of the cases the arrhythmia had been confirmed by the electrocardiogram; in the few exceptions, there was no reasonable doubt regarding the type of arrhythmia. As far as consideration of the clinical investigation combined with the necropsy examination would permit, the grouping of the cases was determined as follows:

Auricular Fibrillation (145 Cases).—Endocarditis (Twenty-Eight Cases): In eleven of these cases there was a definite history of rheumatic fever. The lesions were distributed as follows:

There were fourteen cases of mitral stenosis. In thirteen of these the fibrillation was apparently chronic; in one, it was a terminal event. There were six men and eight women. The youngest patient was 28 years of age, the oldest 72, and the average age was 43.

There were nine cases of combined mitral and aortic endocarditis, in all of which the fibrillation was assumed to be chronic. There were four men and five women. The youngest patient was 31 years of age, the oldest 54, and the average age was 42.

There were three cases of aortic stenosis with calcification of the aortic valve. All were apparently cases of chronic fibrillation, and all patients were men. Two were 62 years of age and one was 64.

33. Butterfield, H. G., and Hunt, G. H.: Observations on Paroxysmal Tachycardia, Quart. J. Med. **7**:209, 1914.

There were two cases of subacute mitral endocarditis. One was rheumatic, the other bacterial in origin. The patients were both men, 21 years of age, who had chronic fibrillation. Most of the hearts in this group showed moderate hypertrophy; in a few it was extreme.

Exophthalmic Goiter (Thirty-Six Cases): The fibrillation was terminal in one case, and presumably chronic in the others. There were eleven men and twenty-five women. The youngest patient was 26 years of age, the oldest 68, and the average age was 45. In general, these hearts were only mildly or moderately hypertrophied.

Adenomatous Goiter with Hyperthyroidism (Twenty-Seven Cases): In three of these, the fibrillation was practically terminal, occurring for only a few days before death; in the others it was supposedly chronic. The diagnosis in one of these cases was questionable so far as the etiology of the cardiac condition was concerned, because the heart was so hugely hypertrophied (weight 848 Gm.). As a rule, these hearts were only moderately hypertrophied. Five of the patients were men and twenty-two were women. The youngest was 47 years of age, the oldest 79, and the average age was 59. These patients were, therefore, considerably older than those with exophthalmic goiter.

Hypertension (Eleven Cases): In these eleven cases, hypertension was without doubt the cause of the cardiac failure. In three other cases, hypertension was assumed to be the cause of the cardiac condition because of the great hypertrophy and the absence of any other etiologic factor, but at the time of examination the blood pressures were normal. Of the eleven reasonably certain cases there were six men and five women. The youngest patient was 42 years of age, the oldest 70, and the average age was 56. The age incidence, therefore, was similar to that of the patients with adenomatous goiter. Of the three patients whose cardiac condition presumably was caused by hypertension, two were men and one was a woman; the ages were 54, 63 and 61, respectively. In all, the fibrillation apparently was chronic. As a rule, these hearts showed little coronary sclerosis, but all were considerably hypertrophied.

Coronary Sclerosis (Four Cases): There were three men and one woman whose ages were 81, 70, 76 and 72, respectively. Three of these hearts were moderately hypertrophied, and the patients also had hypertension. The other heart presumably was of normal size, but the patient had hypertension. These were all supposedly cases of chronic fibrillation.

Chronic Adhesive Pericarditis (Two Cases): These were presumably of rheumatic origin. One patient was a man, aged 57, the other a woman, aged 70. One heart weighed 675 Gm., the other 495 Gm. In both cases, the fibrillation was chronic.

Syphilis (One Case): This patient was a woman, aged 35, with syphilitic aortitis and aortic endocarditis. The fibrillation apparently was chronic.

Combined Conditions (Twelve Cases): In four cases both adenomatous goiter with hyperthyroidism and hypertension occurred. In three cases both hypertension and coronary sclerosis were present, and because of the degree of hypertrophy the hypertension was assumed to be the primary factor. In two cases the patients had both hypertension and endocarditis. In one case there was adenomatous goiter with hyperthyroidism and chronic adhesive pericarditis; in another, exophthalmic goiter and hypertension; in a third, exophthalmic goiter and coronary sclerosis. In the last, the fibrillation was terminal, but in all the others it presumably was chronic.

Absence of Any Related Disease (Thirteen Cases): In these cases the fibrillation was supposedly chronic but an etiologic factor could not be deduced, and the hearts were, as a rule, slightly hypertrophied. There was a history of rheumatic fever in one case. Nine patients were men and four women. The youngest patient was 40 years of age, the oldest 75, and the average age was 54.

Terminal Auricular Fibrillation (Eleven Cases): In most of these cases death followed a major operation, and the fibrillation existed for only a few days before death. The hearts were not appreciably enlarged. There were eight men and three women. The youngest was 29 years of age, the oldest 88, and the average age was 64.

Auricular Flutter.—There were seven cases of auricular flutter. Mitral stenosis existed in one case; adenomatous goiter with hyperthyroidism in one; hypertension in one, and adenomatous goiter with hyperthyroidism and hypertension in one. In two cases a related disease could not be determined, and in one case the patient had an abscess of the lung and cirrhosis of the liver. In one case the flutter had occurred paroxysmally for a year, and in the others it was continuous.

Paroxysmal Tachycardia.—There were only two cases of this arrhythmia. One patient was a man, aged 78, who died from pyelonephritis and bronchopneumonia four days after excision by cautery of an epithelioma of the base of the bladder. He had had paroxysmal tachycardia for twenty years. The heart weighed 465 Gm. and was apparently normal except for one terminal vegetation on the mitral valve. The other patient was a woman, aged 27, whose myocardium was the seat of extensive fibrosis. This was such an unusual case that it will be used as the basis of a separate report.

MICROSCOPIC CHANGES

Twenty-nine of these hearts were selected for special histologic examination. Twenty-six were from cases of auricular fibrillation. Of

these, there were eight cases of endocarditis, six of goiter, six of hypertension, two of coronary sclerosis, one case of chronic adhesive pericarditis, one of syphilis and two cases of terminal auricular fibrillation without assignable explanation. Of the other three, there were two cases of auricular flutter and one case of paroxysmal tachycardia. As controls, thirty-five supposedly normal hearts also were studied.

The following routine method of study was adopted. A block of tissue, about 2.5 by 1 cm., was taken longitudinally along the edge of the crista terminalis just below the orifice of the superior vena cava. A thread was tied through the end nearest the vena cava, and the sections were cut transversely from this end at intervals of 1 mm. This block contained the sino-auricular node. A second block of tissue was excised from the septums of the heart, including part of the interauricular, auriculoventricular and interventricular septums. This block contained the auriculoventricular node and bundle and the first portions of the right and left bundle branches. It was divided into two equal pieces by a vertical incision, and a thread was sewed into the right end of each portion. Sections were taken for microscopic study at intervals of 1 mm. transversely through the two pieces; the ends through which the thread was sewed were used as the tops of the blocks. In this way, a series of sections was made transversely through the auriculoventricular node and bundle and obliquely through the bundle branches.

Two other blocks were removed from the interventricular septum, one on each side, transversely through the regions containing the main right and left bundle branches. These were cut transversely, so that the Purkinje fibers of the bundle branches were seen in cross-section.

In addition, other blocks of tissue were removed from various parts of the heart, one from the wall of the right auricle posteriorly near the right ventricle, one from the left auricle posteriorly near the left ventricle, one from the wall of the right ventricle posteriorly near its middle and one from the left ventricle posteriorly near its base.

All of the blocks of tissue were fixed in a 10 per cent solution of formaldehyde and embedded in celloidin. The microscopic sections were cut 8 microns thick; all were stained with van Gieson's picrofuchsin stain and many with hematoxylin and eosin. In eight supposedly normal hearts and in thirteen of the hearts showing pathologic changes, sections of the right auricle in the region of the sino-auricular node, containing nerve cells or ganglions, were stained with thionin.

Also, frozen sections of the interauricular septum and the left ventricle of all of the hearts were stained with scharlach R. to determine the microscopically visible fat content of the muscle fibers.

Normal Hearts (Controls).—The thirty-five supposedly normal hearts were studied in a similar manner, especially with reference to the histology and anatomy of the sino-auricular node, conduction system and auricles. The histologic and anatomic structure of the sino-auricular node and conduction system, as described by Keith, His, Tawara, de Witt and others, was confirmed. The sino-auricular node (Keith-Flack) was found to be a relatively long, flat bundle of interlacing, thin fibers in a groundwork of connective tissue, situated subepicardially, just below the mouth of the superior vena cava, with its longitudinal axis in the sulcus terminalis. Its cross-section is fusiform or roughly triangu-

lar in shape, and down its middle runs the fairly large artery of the node (fig. 1). There are also a number of arterioles in its substance; nerves and nerve ganglions are found subepicardially in its vicinity, and often nerves are seen at its edge. In only two instances of all hearts examined, however, was a definite nerve cell seen in the substance of the node. Stained with van Gieson's picrofuchsin, the node is easily identified by its compactness, red color due to the large amount of connective tissue, and the centrally placed artery. In good sections, the cross-striations of

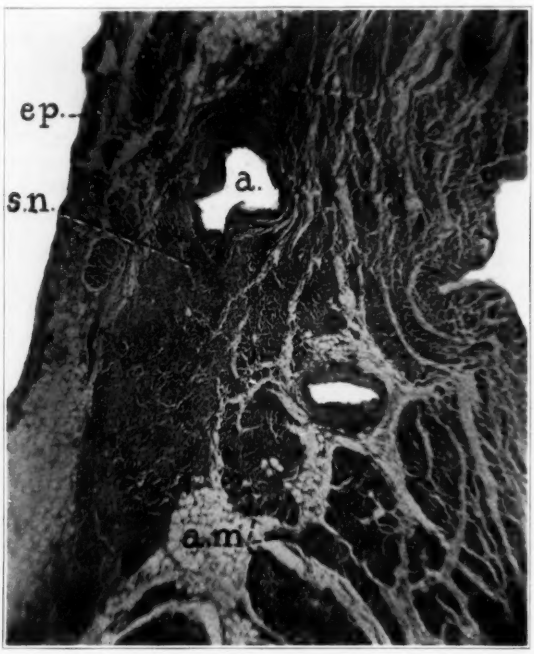

Fig. 1.—Cross-section of the sino-auricular node, *s.n.* (×40). *ep.*, epicardium; *a*, artery of the node; *a.m.*, auricular muscle.

the individual parenchymatous fibers may be seen. In many cases, however, the detail of the individual fibers cannot be ascertained. Also the amount of connective tissue normally present varies within certain limits. The auricular muscle fibers of the crista terminalis often lie close to the node, and occasionally muscle fibers are seen running along its edge. Adipose connective tissue separates the node from the epicardium. The auriculoventricular node (Tawara) lies close to the right side of the posterior portion of the central fibrous body, that is, in the right auricle a short distance anterior to the orifice of the coronary sinus and just

above the attachment of the medial or septal cusp of the tricuspid valve. A relatively large artery lies in its substance (fig. 2). This node is not so compact as the sino-auricular node and contains somewhat less connective tissue. It is flattened out against the central fibrous body, and at its edges the fibers are looser and pass down some distance toward the base of the tricuspid valve. Its fibers are slightly thicker than those of the sino-auricular node, and the cross-striations are more frequently visible. The fibers are arranged in whorls. The artery of this node finally leaves it and passes through the central fibrous body and down into the musculature of the ventricular septum. The node also invades

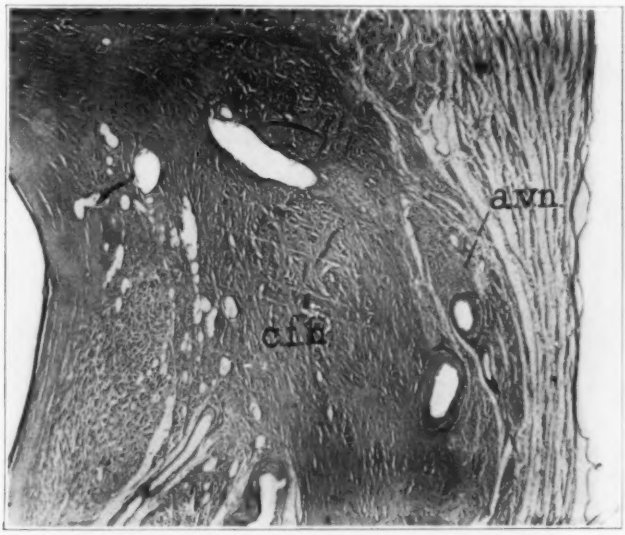

Fig. 2.—The auriculoventricular node; *a.v.n.*, in cross-section, lying against the central fibrous body, *c.f.b.* (×20). The artery to the node has divided into two branches.

the central fibrous body and merges into the auriculoventricular bundle (Kent, His), which runs obliquely downward in the substance of the central fibrous body and membranous septum at the base of these structures and is separated by a little of the fibrous tissue from the interventricular muscular septum (figs. 3 and 4). The fibers are larger than those of the auriculoventricular node and run in parallel bundles. They resemble more the ventricular muscle fibers but do not contain so much myoplasm. The connective tissue framework is delicate, and there is no main artery but a number of arterioles and venules. On cross-section the bundle is roughly triangular, with blunt corners, and the apex

is toward the auricular portion of the heart. Often a fair amount of adipose connective tissue is present. The bundle runs for about from 1 to 1.2 cm. and divides into its right and left branches (fig. 5). The right branch appears to be a continuation of the bundle and passes downward beneath the juncture of the medial and anterior cusps of the tricuspid valve as a white, threadlike or nervelike process a short distance beneath the endocardium and not distinctly separated from the surrounding heart muscle (figs. 6 and 7). This branch is often difficult to recog-

Fig. 3.—The beginning of the bundle of His, *a.v.b.*, in cross-section, as it lies in the edge of the membranous portion of the interventricular septum, *m.s.* (×20).

nize microscopically in the human heart; in fact, I have had more success in gross dissections than in the histologic examination of this branch. The fibers closely resemble the muscle fibers. The right branch passes directly along the trabeculum, which corresponds to the moderator band of the calf heart, to the anterior papillary muscle of the right ventricle. In the cross-sections of the auriculoventricular bundle its origin is often difficult to recognize unless serial sections are made, because it is so small and is cut obliquely in the routine method employed. The left branch is given off at the same point, but it flattens out immediately under the

endocardium of the left ventricle just below the aorta; so in the method employed in this study it is always seen, and is present in all of the sections beyond the point where the branch begins (fig. 8). The part of the main bundle from which the two branches have their origin is known as the crus communis and is triangular on cross-section, the two inferior angles representing the points of origin of the bundles. The origin of the right branch, when seen, passes out superficially through the ventricular muscle, but the origin of the left is even closer to the

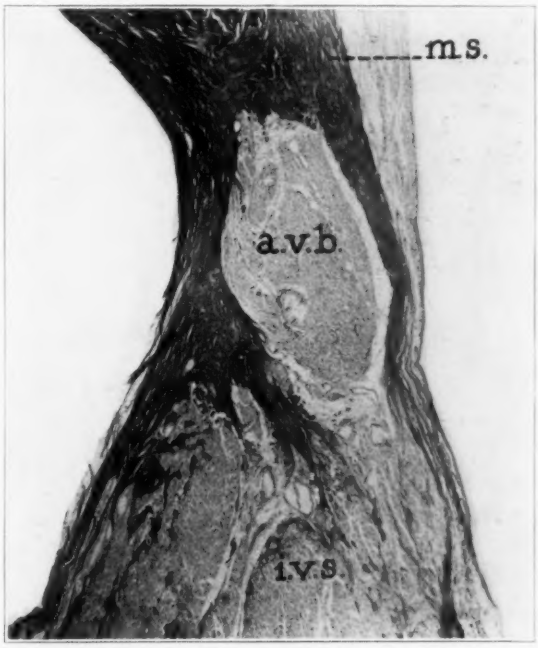

Fig. 4.—The bundle of His, *a.v.b.*, in cross-section farther along than in figure 3, lying in the membranous portion of the interventricular septum, *m.s.* (×20); *i.v.s.* muscular portion of interventricular septum.

endocardium; the Purkinje fibers are directly beneath the endocardium and usually are distinctly separated from the heart muscle. The Purkinje fibers are broader and paler than the muscle fibers and anastomose somewhat less profusely (fig. 9). The cross-striations are usually not so distinctly seen as in the ventricular muscle, and the myofibrils are more prominent. On cross-section the Purkinje fibers are larger and paler, but are similar to the muscle fibers (fig. 10).

The auricular muscle fibers are more wavy, less compact and less anastomotic than the ventricular muscle fibers. These fibers are also usually paler; their myofibrils (the longitudinal lines) are often prominent; the cross-striations may be faint, are sometimes invisible, and often when seen are broken and more prominent at the edge of the fibers. The nuclei are often distorted. The auricles contain considerable subepicardial adipose connective tissue, and in fixation apparently there is more shrinkage and distortion of the sections of the auricle on this

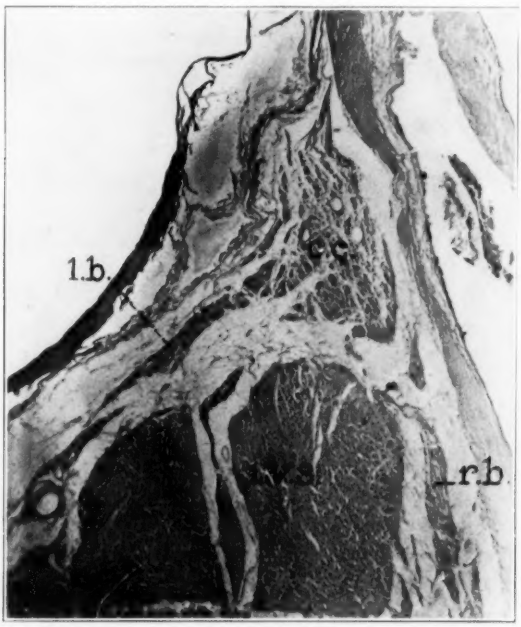

Fig. 5.—The crus communis, *c.c.*, in cross-section, with the origin of the left bundle branch, *l.b.*, and the right bundle branch, *r.b.* (× 20).

account. The epicardium itself is usually thin. The endocardium of the auricles is thick. Adipose connective tissue is not present between the muscle fibers and the endocardium. Often there are a few small lymphocytes in the epicardium. Often the auricular muscle fibers appear to be swollen, in which case they are pale and may contain a large central space apparently devoid of cytoplasm in which the nucleus lies. Frothingham called attention to this and noted that such appearances were also present in some normal hearts. This is undoubtedly true and these phenomena can, therefore, be exonerated as playing a rôle in the mechanism of arrhythmia.

The histology of the ventricles is better known, because routine sections from them are more frequently studied. The sections are always more satisfactory than those of the auricles, perhaps because one presupposes that the sections of the auricle should appear like those of the ventricle. The muscle fibers are darker and more compact, with indistinct myofibrils, but usually there are sharp and regular cross-striations when viewed with subdued light. The nuclei usually are not distorted. The endocardium of the ventricles is rather thin, as opposed to the thick

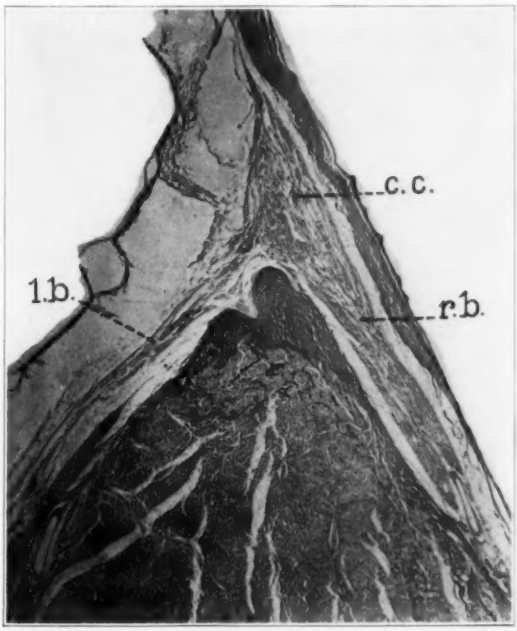

Fig. 6.—A little farther along than figure 5, showing the origins of the bundle branches more clearly (×20).

endocardium of the auricles. The individual Purkinje fibers cannot usually be recognized.

Endocarditis.—The group of hearts in which fibrillation occurred in life comprises eight cases of endocarditis and one case of adhesive pericarditis; the latter is considered in this group because of the supposedly similar etiology. There were three cases of mitral stenosis, one case of aortic stenosis with slight involvement of the mitral valve, three cases of combined mitral and aortic stenosis, one case of subacute rheumatic mitral endocarditis and the one case of chronic adhesive pericarditis.

Four patients were men and four women. All were less than 46 years of age except the patient with aortic stenosis who was a man, 54, with calcification of the aortic valve and the patient with chronic adhesive pericarditis who was a man, aged 57. Six patients died of cardiac decompensation directly, one of cerebral embolism complicating decompensation and one of mesenteric thrombosis. The duration of the auricular fibrillation could not be ascertained definitely in any case. This group, as a whole, showed more definite lesions than any of the other

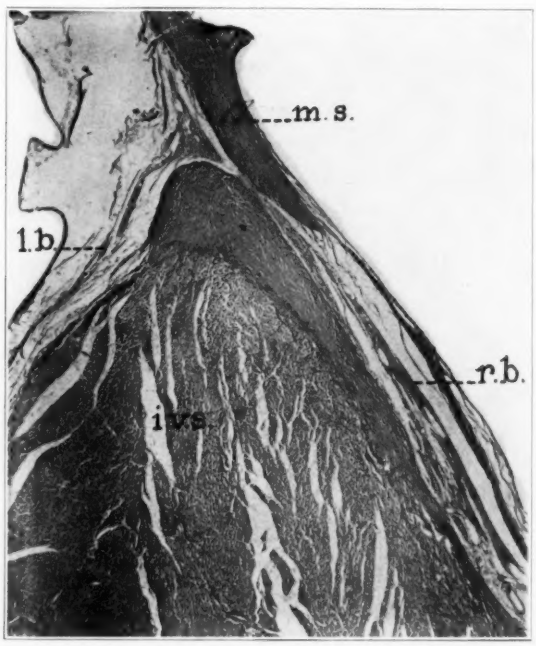

Fig. 7.—A short distance farther along than figure 6, showing that the bundle of His divides into the two bundle branches, *l.b.* and *r.b.* (×20).

groups. In the sino-auricular node the only features of note were an apparent slight increase in connective tissue in one case and a moderate increase in another. In four there were small foci of connective tissue. In one case there were a few small lymphocytes scattered through the node, and in another some small foci of lymphocytes. In one case the nodal fibers were separated more than usual, in one they were less interlacing and in another there appeared to be a diminution in the number of fibers. The detail of the individual fibers was not good in four cases. There was congestion of the node in one instance. The epicardium in

the region of the node contained small lymphocytes in four cases; in two they were few in number; in another they were scattered throughout, and in the fourth they were numerous and collected mainly about blood vessels. Aschoff-like bodies were present in the epicardium and also in the myocardium of the right auricle in only one case, that of a young man, aged 21, with subacute mitral endocarditis whose cardiac symptoms were of nine months' duration, although he had had rheumatic fever nine years before. The epicardium was thickened in one case,

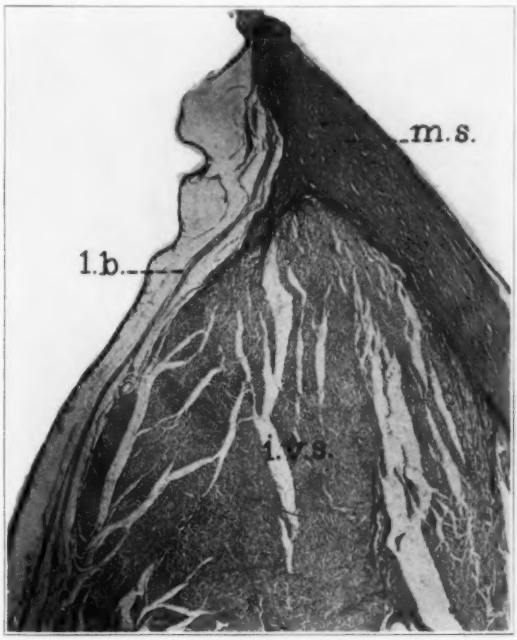

Fig. 8.—A short distance farther along than figure 7. The right bundle branch is no longer seen, but the left bundle branch, *l.b.*, being broad and flat, is still present in the section (×20).

and epicardial adhesions occurred in the case of adhesive pericarditis. In three cases there were small lymphocytes in the subepicardial connective tissue, but they were present in large numbers in only one case. Subepicardial hemorrhages were noted in two cases. The muscle fibers of the heart were universally swollen in the region of the node in two cases, and swollen in places in one case. The cross-striations of the muscle fibers were not seen in three cases. The auricular muscle fibers in the other sections of the right auricle were swollen universally in one

case and irregularly in two cases. Cross-striations were practically absent in four cases and present only here and there in another case. The myofibrils were prominent in seven cases.

In one case the auriculoventricular node contained some small lymphocytes together with a few scattered polymorphonuclear leukocytes. The artery of one of the nodes was thickened but was not fibrotic. The auriculoventricular bundle showed shrinkage of its fibers in one instance. Small lymphocytes were scattered throughout the auriculo-

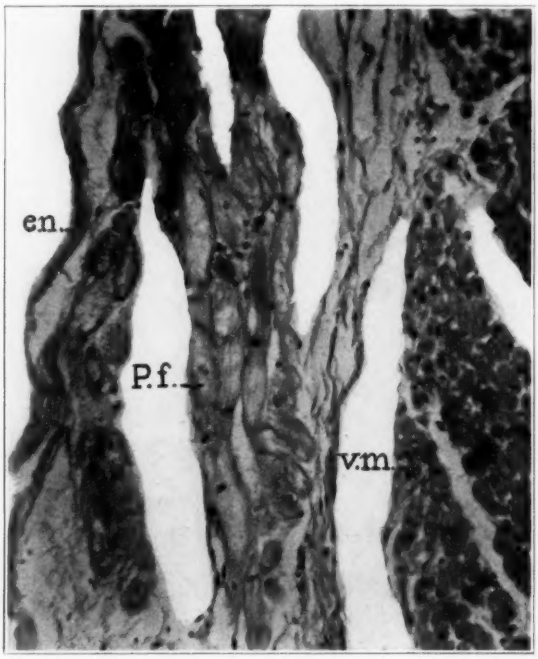

Fig. 9.—The posterior limb of the left bundle branch, showing the Purkinje fibers, *P.f.*, in longitudinal section beneath the endocardium, *en.*, and the ventricular muscle fibers, *v.m.*, in cross-section (× 150).

ventricular bundle in one case, and Aschoff-like bodies were in the bundle in the case of subacute endocarditis. In none of the cases did the bundle branches show any features of note, and the right branch was identified in only three cases.

Sections of the left auricles showed even less frequent lesions, which were unimportant and were not of sufficient interest to enumerate. The same general characteristics of the muscle fibers prevailed as in the right auricle. The main points of difference between the two were the less

frequent occurrence of lymphocytes and the more frequent thickening of the endocardium in the left auricle.

In the sections of the ventricles there were no lesions of note except Aschoff nodules in one case. Increase in connective tissue or thickening of the arteries was not noted except in one case in which there was slight thickening and fibrosis of the larger arterioles.

The sections stained for fat showed accumulation of small fat droplets in the muscle fibers of both auricle and ventricle in five cases, and

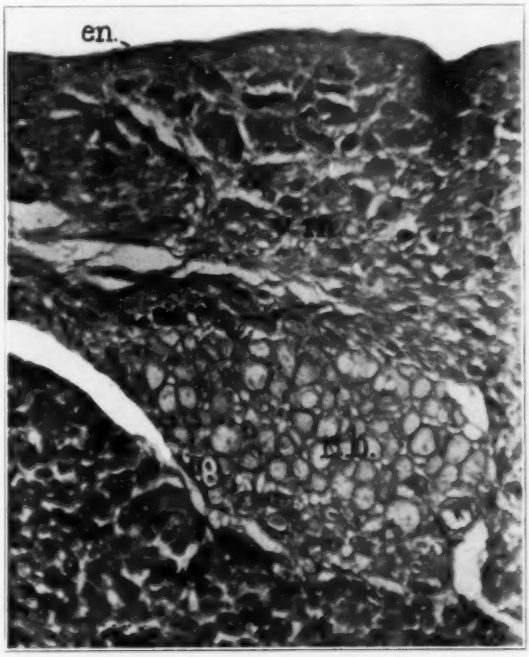

Fig. 10.—Through the "moderator band" of the right ventricle, showing the small right bundle branch, *r.b.*, in cross-section, surrounded by the ventricular muscle, *v.m.*, and lying some distance beneath the endocardium, *en.* (× 150).

in general the amount of fat was approximately the same in the auricle and ventricle. In one case there was a moderate accumulation of fat droplets in the auricle and none in the ventricle. In three cases there was no demonstrable fat in either auricle or ventricle.

Goiter.—There were six cases of exophthalmic goiter and two of adenomatous goiter with hyperthyroidism. Of the cases of exophthalmic goiter, four occurred in men and one in a woman. The ages of the patients ranged between 58 and 72, except one (32 years). Only one

died directly of cardiac decompensation. The largest heart weighed 423 Gm. One patient had coronary sclerosis, graded 3. Both of the patients with adenomatous goiter were women, one aged 60 and one aged 49. Both had hypertension in addition to thyrotoxicosis. One died following embolectomy of a femoral artery, the other died of cardiac decompensation three days after subtotal thyroidectomy. One heart weighed 463 Gm., the other 357 Gm. The exact duration of the auricular fibrillation could not be ascertained in any case. The histologic alterations of this group were even less marked than in the group with endocarditis. The sino-auricular node showed few changes. In one, the fibers were swollen and pale, corresponding with the auricular muscle fibers. In one, the muscular coat of the nodal artery was moderately thickened, but was without fibrosis. In another, as the end of the node was reached, there appeared a loose network of connective tissue with a few scattered small lymphocytes. The auriculoventricular node apparently was normal in all but one case, in which there was slight fibrosis of the nodal artery. In one case the bundle of His was more vascular than usual, and in another it was markedly congested; this condition involved the adjacent region of the interventricular septum also. The fibers of one were separated into definite fasciculi and were pale; some were swollen, and others were shrunken. The bundle branches were all normal except that in one case, at the origin of the right branch, there was in one area a small group of polymorphonuclear leukocytes with a few histocytes; the right branch was recognized, however, in only two cases. The muscle fibers of the right auricles did not show more changes than are usually seen in a similar group of normal hearts. In two cases the fibers were swollen and pale with prominent myofibrils and indistinct cross-striations, in two they were not swollen but the fibers had prominent myofibrils and invisible cross-striations, and in two the fibers were cloudy or homogeneous without visible cross-striations. In one case there were some small lymphocytes in the subepicardial fat, near the sino-auricular node, and some connective tissue replacement of the muscle fibers, and in three there were a few small lymphocytes in the epicardium near the node. In general, the muscle fibers of the left auricle were similar to those of the right, although they were not swollen as often. The ventricles showed few features of note. In the case of toxic adenoma there was an area of calcification in the membranous septum and an area of infarction in the left ventricle, and the cross-striations were distinct only in the left ventricle. A few small lymphocytes, polymorphonuclear leukocytes and plasma cells were present in the edematous subepicardium of the right ventricle in one case, and a few small lymphocytes and plasma cells in the subendocardium of the right ventricle in another. In one case there were a few small lymphocytes in the epicardium of the left ventricle. The ventricular muscle

fibers of one heart appeared to be slightly granular, with prominent myofibrils. Demonstrable fat was not present in the muscle fibers of the auricle in two cases, a mild to moderate amount, in three, and patchy, heavy infiltration in two. The ventricles showed little if any visible fat in all cases and a mild to moderate amount of lipochromatic pigment in five.

Hypertension.—Six hearts were studied. In one there was evidence of old mitral endocarditis, which, however, had produced hardly any distortion of the valve, and in another there was coronary sclerosis, graded 3. Four of the patients were men and two were women, ranging in age from 42 to 81 years. Four died directly of cardiac decompensation, one of decompensation and grand mal, and one of mesenteric thrombosis complicating decompensation. Auricular fibrillation was known to have existed more than nine months in one case and more than two years in another. In the remainder, its duration was not known. The smallest heart weighed 410 Gm. and the largest, 795 Gm. Inspection did not reveal abnormal fibrosis in any case. The sino-auricular node had thickened arterioles with reduction of their lumina in one case; in one case the arterioles were slightly thickened, and in another they were questionably thickened. The walls of some of the larger arterioles were thickened in one case. In the auriculoventricular node of one heart the arterioles were thickened, with almost obliterated lumina, and in the same node the larger vessels showed subintimal fibrosis. In one case the media of the arteries was somewhat thickened, and in another there was some fibrosis of the media of the main nodal artery. The vessels of the auriculoventricular bundle were not thickened in any case, but there were many blood vessels and much adipose connective tissue (50 per cent) in one, and in the crus communis of another there was some increase in the fat. The bundle branches did not show anything of note; the right bundle branch was recognized in five instances. A few small lymphocytes were present in the epicardium or subepicardium of the right auricle, in the region of the sino-auricular node, in four hearts, and were grouped near some of the larger arterioles in one of these. In one case, there were groups of small lymphocytes in the subendocardium, near the same node. The cross-striations of the muscle fibers of the right auricle were indistinct in two cases, and in two the fibers were swollen and pale. The arterioles of the right auricle were slightly thickened in one case. A patch of calcium deposit was present in the base of one mitral valve. The muscle fibers of the left auricle were swollen, with prominent myofibrils in one case, and the cross-striations were not visible in another. The endocardium was somewhat thickened in one left auricle; in another heart there were some small lymphocytes in the epicardium. The arterioles were slightly thickened in the ventricles in two cases, and there was some increase in

fibrous connective tissue in the interventricular septum in another. Deposits of calcium were present along the lower edge of the membranous septum in one heart. An appreciable increase of connective tissue was not present in any case. Fat was not visible in the muscle fibers in either auricle or ventricle in three cases, or in the auricle of one other case in which there was a slight amount in the ventricle. In one case there were patches of fatty change in both auricle and ventricle and moderate diffuse infiltration of the fibers of both auricle and ventricle in another. Lipochromatic pigment was not prominent in any case, but was seen in a small amount in two cases.

Coronary Sclerosis.—Two cases were studied. One patient was a man, aged 70, who died of pyelonephritis following prostatectomy; he also had hypertension. The heart weighed 552 Gm., and the coronary sclerosis was graded 4. The other was a woman, aged 72, who died of empyema of the gallbladder associated with cardiac decompensation; she also had hypertension. The heart weighed 290 Gm., and the coronary sclerosis was graded 3. The fibrillation apparently had existed for some time in both cases. In one of these the artery of the sino-auricular node was somewhat thickened, and there was some subintimal fibrosis. In the other, the nodal artery showed moderate thickening of the intima; the fibers of the node were larger than usual, resembling more nearly cardiac muscle, and in the substance of the node were some groups of large histiocytes full of dark brown pigment granules, with scattered small lymphocytes in other parts. The auriculoventricular node of one had a nodal artery somewhat thickened with subintimal fibrosis, and the artery of the other also showed thickening of the intima. A tiny bit of calcium was present in the fibrous septum in the region of the left bundle branch in one case. The bundle branch appeared normal in one case but was not seen in the other. In the right auricle of one heart the cross-striations were not visible; in the other the myofibrils were unusually prominent, and there was an increase in intercellular connective tissue in the region of the sino-auricular node. The left auricle was similar to the right in both cases. The ventricular muscle fibers were swollen, and there were indistinct cross-striations in one heart. A moderate degree of fatty change was present in the muscle fibers of both auricle and ventricle in one case, but in the other case a change did not occur in either.

Syphilis.—The patient was a woman, aged 35, who had a definite syphilitic infection of the central nervous system and the classic signs of aortic regurgitation. She died suddenly during a course of antisyphilitic treatment. The arrhythmia was apparently of long standing. The heart was markedly enlarged with severe syphilitic involvement of the aorta and aortic valves. Considerable coronary sclerosis and dilatation of the left ventricle were present. The sino-auricular node and

the auriculoventricular node appeared normal. The left bundle branch appeared normal also, but its origin was surrounded by many small lymphocytes and a few plasma cells. These cellular elements were seen in the connective tissue in all of the sections showing the interventricular septum and were most numerous about some of the arteries; they were less numerous in the other sections of the ventricles. In one area, between the membranous septum and the auricular muscle were a number of small lymphocytes and a few plasma cells. In the connective tissue of the left auricle, especially in the subepicardial fatty tissue, were a great many plasma cells, some of which had two or three small nuclei; there were also some large pale cells undergoing mitotic division. The auricular and ventricular muscle fibers appeared normal. There was practically no fat in the muscle fibers of either auricle or ventricle.

Terminal Fibrillation.—One of the patients was a man, aged 29, with Hodgkin's disease; the other was a man, aged 57, who died of a traumatic subdural hemorrhage. The fibrillation in both cases developed a short time before death. Both of the hearts appeared grossly normal, except for some dilatation of the right auricle in each. The two hearts, microscopically, showed little of note. There was apparently an increase of fibrous tissue in the sino-auricular node in one heart; the auricular fibers in this case were swollen and pale with clear centers, prominent myofibrils and indistinct cross-striations. A little fat was present in the muscle fibers of the auricles and ventricles of both hearts. Lipochromatic pigment at the nuclear poles was seen in small amounts in one case.

Auricular Flutter.—Two cases were studied. Both patients were women, one 58 years of age and the other 65. Both had had hypertension for years and had died of cardiac decompensation. One had an adenomatous goiter also, which was believed to be toxic. The heart of this patient weighed 417 Gm., and that of the other 684 Gm. Except for a few small lymphocytes beneath the epicardium near the sino-auricular node and adipose connective tissue (50 per cent) in the crus communis of the bundle of His near the origin of the two bundle branches, one heart appeared to be normal in every respect. The other likewise showed little of note.

Paroxysmal Tachycardia.—The heart studied was that of a man, aged 78, who had had paroxysmal tachycardia for twenty years. He died of pyelonephritis following cauterization of an epithelioma of the base of the bladder. This case is referred to also in the analysis of cases under paroxysmal tachycardia. The heart weighed 465 Gm. and appeared normal except for a small terminal vegetation on the mitral valve. The sections did not show abnormalities of note, except for the presence of a small deposit of calcium high up in the central fibrous body near the auriculoventricular node, with a few small lymphocytes and plasma

cells nearby. A moderate amount of lipochromatic pigment was present at the poles of the nuclei of the ventricular muscle fibers.

Nerve Cells.—A special study was made to determine whether there were any changes in the nerve cells or ganglions in the region of the sino-auricular node. Sections containing nerve cells or ganglions were stained with thionin in eight supposedly normal hearts and in thirteen of the cases of auricular fibrillation. No difference in this respect was observed between the normal and pathologic hearts.

COMMENT

Several points with reference to the fundamental basis of auricular fibrillation in the series of 145 necropsies warrant emphasis. Chronic endocarditis, exophthalmic goiter and adenomatous goiter with hyperthyroidism were the three conditions most frequently encountered, representing 19, 25 and 19 per cent, respectively, of the entire number of cases, or a combined total of 63 per cent. The high incidence of cases of goiter is due in part to the fact that many of them were drawn from a large surgical goiter clinic. The percentage of cases of endocarditis is perhaps far too low because of the policy of returning patients with this condition to their homes if they cannot be materially benefited by treatment in hospital. Therefore, those on whom necropsies were performed were usually those who were too ill to be returned home. Nevertheless, these percentages indicate the types of heart disease in which auricular fibrillation is most likely to occur. Of the three conditions, endocarditis is perhaps most readily diagnosed by the average clinician, so that in the absence of evidence of endocarditis, one should next consider the possibility of hyperthyroidism.

Heart disease due to hypertension constituted 8 per cent of the cases if only those cases are included in which hypertension was known to have existed. This figure becomes 10 per cent, if the three cases are added in which the previous existence of hypertension could not be established. The average size of these hearts was much larger than those in the cases of hyperthyroidism, and in the absence of evidence of endocarditis or hyperthyroidism, hypertension should be considered as an etiologic factor when there is auricular fibrillation and a considerably enlarged heart, even though the hypertension cannot be established. Coronary sclerosis, chronic adhesive pericarditis and syphilis are rather unusual sources of auricular fibrillation.

In about 8 per cent of the cases there were two distinct etiologic factors. Although both contributed to the breakdown of the heart, it was usually one which caused the initial strain and the other which served as the "straw that broke the camel's back." When hypertrophy of the heart in a case of hypertension is accompanied by severe coronary sclerosis, it is logical to assume that the hypertension existed for a long

time prior to the development of the coronary sclerosis, because continued hypertrophy is not consistent with an impaired coronary circulation. A relatively common combination of etiologic agents in this group seems to be toxic adenomatous goiter and hypertension. Both of these conditions may exist a long time before injury to the heart is demonstrable, and it is usually impossible to decide which is the more important as regards the development of the cardiac condition. There is no question, however, that removal of the toxic adenomas, if possible, is of great advantage to the overburdened heart.

Except for the eleven cases of terminal auricular fibrillation, a condition which is not of great practical importance, there still remained a group of about 9 per cent of cases of established fibrillation in which a cause for the cardiac condition was not apparent. In most of these the status of the heart was considered to be of secondary importance to some more serious condition. In fact, cardiac symptoms were often mild.

From the small series of cases of auricular flutter, conclusions cannot be drawn as to the incidence in different types of heart disease. Endocarditis, hyperthyroidism and hypertension were the only definite types observed. One of the two cases of paroxysmal tachycardia, like the majority of such cases, occurred in a heart which had been subject to none of the etiologic factors in heart disease. The other was an unusual case of extensive myocardial fibrosis in a young adult.

The microscopic study of the twenty-nine hearts which had been the seat of these arrhythmias was strikingly negative as regards any distinctive lesion or, in fact, as regards any changes which could be assigned as the cause of the arrhythmia in any individual case. This was true not only for the types of arrhythmia, but also for the different types of heart disease. The lesion which Frothingham called attention to, namely, edema and vacuolization of the auricular muscle fibers, was observed about as often in the control group as in the affected hearts. On the whole, there was more evidence of disease in the region of the sino-auricular node than in other places, but even this was only slight or moderate in degree. The region of the orifices of the venae cavae has been called the sewer of the heart because of the frequently observed lesions there. None of the severe lesions of the sino-auricular node, such as cellular infiltration, degeneration or sclerosis, which were observed by some of the earlier investigators, was noted in this series.

If one accepts the conclusion drawn from this study that a specific histologic picture of auricular fibrillation or allied arrhythmias does not exist and further accepts the work of Lewis on the physiology of these arrhythmias, hypotheses are then in order concerning their cause. That there is a common cause in most cases of auricular fibrillation seems evident from the results of treatment by quinidine which is

apparently of similar efficacy in different types of heart disease, except perhaps in cases with hypertension. It is difficult to conceive that quinidine could alter the structure of the cells, at least as quickly as it sometimes acts. Some change possibly occurs in the chemical or physiochemical composition of the muscle fibers, at least in auricular fibrillation, which increases their refractoriness and causes reduction in the rate of conduction of an impulse. Possibly some vagal effect may cooperate with such change to bring about these conditions. Why the auricles and not the ventricles should fibrillate is another point to be considered, and this feature is the one which probably led Koch and others to attach such importance to the effect of dilatation of the right auricle. Furthermore, one has also to explain why the main path of the circus movement should be the region about the mouths of the venae cavae. This is probably due to some anatomic factor. Again, it is not easy to account for the occurrence of fibrillation in compensated cardiac conditions as well as in decompensation, and paroxysmal fibrillation and flutter befog the issue even more. All that can be said at the present time is that there is some unknown factor or a number of factors which bring about an identical disturbance in function of the auricular muscle fibers without associated structural changes.

SUMMARY AND CONCLUSIONS

A series of 145 cases of auricular fibrillation, 7 cases of auricular flutter, and 2 cases of paroxysmal tachycardia, all with necropsies, was studied from the standpoint of etiology and pathology. All the usual types of heart disease were found; cases of endocarditis and hyperthyroid states were the most numerous. Hypertension was found to be a common condition, but the occurrence of auricular fibrillation in other types of heart disease was uncommon. In about 8 per cent of the cases of auricular fibrillation there was a combination of possible etiologic factors, and in about 9 per cent an etiologic factor could not be suggested.

Twenty-nine hearts which had been the seat of these arrhythmias were studied microscopically. A distinctive lesion for the arrhythmia was not found, and the lesions were not considered in themselves of sufficient importance to account for the arrhythmia. There apparently is not, therefore, a specific histologic syndrome in auricular fibrillation and probably none in auricular flutter and paroxysmal tachycardia.

THE VARIABILITY OF BLOOD PRESSURE

MORNING AND EVENING STUDIES *

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Studies such as those recently made by Alvarez,[1] and Diehl and Sutherland,[2] in which a surprisingly large number of presumably normal young adults are reported with elevation of blood pressure, lead one to wonder what proportion of these high readings can be attributed to normal fluctuations or variations of the blood pressure. Unquestionably many of the persons who show high pressures during required examinations of a group usually give normal readings; in fact, by taking repeated readings of the blood pressure of those university students who, on entrance examinations, had systolic pressures of 140 mm. or more, Diehl and Sutherland [2] found that the pressures of only 15 per cent of this group persisted at that high level. Other students showed high readings on some occasions and low readings on others, while the largest proportion were above "normal" on only the initial reading. In all groups, however, there were sufficient variations of pressure to raise the following questions: Is it normal for young adults to have these fluctuations of blood pressure and how much fluctuation is necessary to constitute an abnormality?

Peters [3] concluded, from observations on blood pressure in 1,500 subjects, that in healthy persons less than 20 years of age the normal systolic pressure may vary from 60 mm. plus one-half the age to 100 mm. plus one-half the age, and that in persons more than 20 years of age the variation may be from 90 mm. plus one-half the age to 130 mm. plus one-half the age. In other words, he feels that in young people an individual variation of 40 mm. is within normal limits. Hare [4] studied individual variations by taking four consecutive readings of the blood pressure after his subjects had rested for twenty

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1. Alvarez, W. C.; Wulzen, R., and Mahoney, L. J.: Blood Pressure in Fifteen Thousand University Freshmen, Arch. Int. Med. **32**:17 (July) 1923.

2. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men, Including a Special Study of Those with Hypertension, Arch. Int. Med. **36**: 151 (Aug.) 1925.

3. Peters, J. T.: Die Diagnostik von Hypertension bzw. Hypertension des systolischen und diastolischen Blutdruckes, München med. Wchnschr. **72**:503 (March 27) 1925.

4. Hare, D. C.: The Variations of Blood Pressure Readings Studied Under Uniform Conditions, Proc. Roy Soc. Med. **19**:36, 1926.

minutes on a couch. The first reading was discarded and the variation between the next three readings computed. With sixty patients in 228 sittings, he found between the three readings a variation of more than 10 mm. in 29.4 per cent of the sittings, of 15 mm. or more in 11.9 per cent and of 20 mm. or more in 1.3 per cent. Brooks and Carroll [5] found the maximum pressure of the day between four and five o'clock in the afternoon and, after a night's sleep, an average drop of 16.5 mm. in thirty patients with a mean pressure of 100 mm.; a drop of 24 mm. in sixty-eight patients with a mean pressure of 142.5 mm., and a drop of 44.8 mm. in twenty-nine patients with a mean pressure of 204.5 mm. Kinney,[6] in discussing factors which influence blood pressure, stated that blood pressure frequently does not run a "constant course but jumps about the scale in an erratic manner," and that this condition is not limited to persons of a nervous temperament. Sigler [7] cited several cases of hypertension with systolic pressures showing variations of from 30 to 65 mm.; he stated that "it would seem that variations of this kind, as well as hypertension in general, are dependent upon some structural or functional abnormality of the vegetative nervous system exhibiting itself in the form of vasomotor pressor effects." Luisada [8] noted in normal persons a nocturnal lowering of systolic pressure of from 15 to 20 mm. and a simultaneous rise of from 10 to 20 mm. in diastolic pressure. Hourly variations, he said, may differ in intensity in different circulatory syndromes and in different illnesses.

EXPERIMENTAL PROCEDURE

Technic.—These studies of the variability of the blood pressure, which answered some questions and raised others, led me to undertake some additional observations on variation in blood pressure in normal persons under normal conditions. The group studied consisted of 100 male students of the University of Minnesota. Readings were taken in the morning and evening of each day for six consecutive days. The morning readings were made between the time of rising and that of breakfast, the intent being to record the pressure at the beginning of the day's activity, not necessarily the minimum pressure for the day. The evening readings were taken just before dinner, at the close of the day's activity. Readings were made with the subject sitting on a chair. Three senior medical students assisted in taking the readings but each observer took all readings on the cases assigned to him, and identically the same technic was followed by each one. Mercury manometers and the auscultatory method were used throughout.

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5. Brooks, H., and Carroll, J. H.: A Study of the Effects of Sleep and Rest on Blood Pressure, Arch. Int. Med. **10**:96 (Aug.) 1912.

6. Kinney, V. C.: Blood Pressure: Some Original Observations, J. A. M. A. **83**:1420 (Nov. 1) 1924.

7. Sigler, L. H.: Periodic Variability of Arterial Hypertension, Am. J. M. Sc. **172**:543 (Oct.) 1926.

8. Luisada, A.: Le variazioni orarie della pressione arteriosa, Riforma med. **41**:817 (Aug. 31) 1925.

Analysis of the Group.—The 100 students on whom the observations of the present study were made were unselected except in that they all belonged to fraternities, and a considerable proportion of them were medical students. The readings all were made at the fraternity houses. The mean age of the group was 22.71 ± 0.17 years; the mean weight, 148.00 ± 0.64 pounds, and the mean height, 68.52 ± 0.196 inches. Taking as the pressure for each student the average of all the readings taken on him, the mean pressure for the group was 119.15 ± 0.47 mm. In studies of the blood pressure of freshmen entering the university, Diehl and Sutherland [2] found in the age group of 22 years a mean systolic pressure of 122.6 ± 0.50 mm. and in that of 23 years a mean pressure of 123.3 ± 0.67 mm. In students with a mean age of 20.078 ± 0.046 years, Jackson [9] found a mean weight of 141.44 ± 0.29 pounds and a mean height of 68.684 ± 0.042 inches. From these comparisons it would seem that the present group was not abnormal in any way but was truly representative of the older portion of the university students.

Morning Pressures.—As previously stated, the morning readings of pressure were made on each of six consecutive days at the beginning of the day's activity. The mean of these morning systolic pressures in the 100 subjects was 114.94 ± 0.34 mm. As a measure of the variability of the morning pressure in an individual subject, the standard deviation from the mean of the six morning readings taken on the case was computed. Then the mean of all these morning standard deviations for the 100 subjects was calculated and found to be 5.57 ± 0.167 mm.; the mode was 4.5 mm. and the median, 5.25 mm. The distribution of the morning standard deviations is shown in chart 1 A.

The range of blood pressure, that is, the difference between the lowest and the highest readings, although not an accurate statistical measure, was computed because it is in these terms that the average practitioner thinks of variation in blood pressure. The morning range in individual cases has been portrayed graphically in chart 2 A. The lowest morning range over the six day period was 1 mm.; the highest, 39 mm.; the mean, 16.29 ± 0.486 mm.; the mode, 16 mm., and the median, 16 mm. With the mean, mode and median so nearly identical for both range and standard deviation, the distribution curves are regular and probably truly representative for such a group.

Evening Pressures.—The evening pressures were taken at the end of the day's activity and for the group as a whole showed a mean pressure of 124.37 ± 0.29 mm. The standard deviations of the evening

9. Jackson, C. M.: The Physique of Male Students at the University of Minnesota: A Study in Constitutional Anatomy and Physiology, Am. J. Anat. **40**: 59 (Sept. 15) 1927.

readings from the evening mean of each subject are shown in a distribution chart, chart 1 *B*. The mean of all these individual evening standard deviations was 5.86 ± 0.21 mm.; the mode, 3.5 mm., and the median, 6 mm.

The minimum evening range in any subject was 2 mm.; the maximum, 38 mm.; the mean, 17.86 ± 0.616 mm.; the mode, 22 mm., and

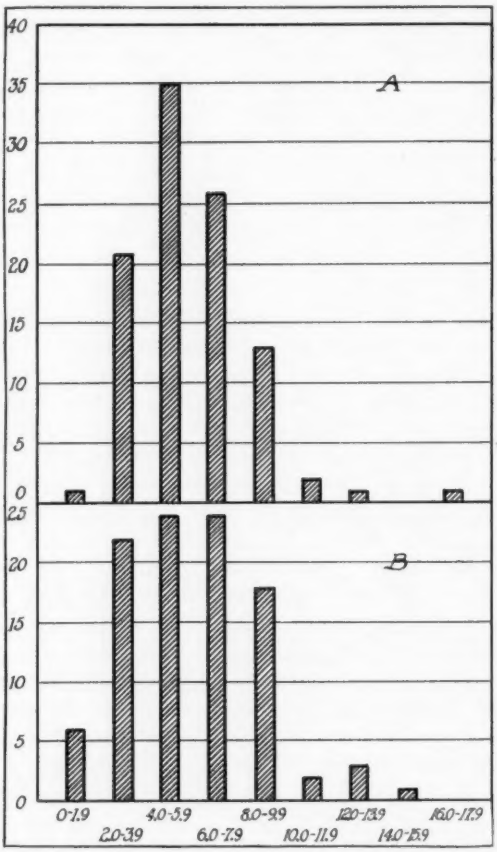

Chart 1.—*A* gives the standard deviation of the six morning readings on each subject from the mean of these six readings; *B*, the same for the evening readings. The vertical scale at the left indicates the number of subjects.

the median, 16 mm. Chart 2*B* shows the distribution of the range in evening blood pressure in the individual subjects.

Comparison of Morning and Evening Readings.—The mean of the morning readings was 114.94 ± 0.34 mm. and of the evening readings,

124.37 ± 0.29 mm., a difference of 9.43 ± 0.44 mm. Since the actual difference shown is more than twenty times the probable error of the difference, the significance of the observation is beyond question and indicates that in this group the day's activity tended to increase the systolic blood pressure 9.43 ± 0.44 mm. In a study of recruits at Camp Lewis, Addis [10] found a mean pressure, in bed, of 99 mm., with an increase to 127 mm. during the day's activities.

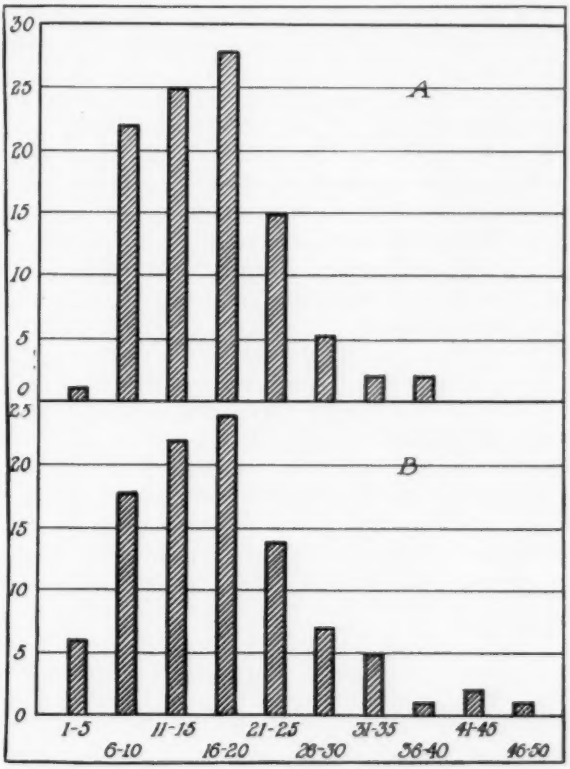

Chart 2.—*A* gives the range in morning readings of blood pressure on the individual subjects; *B*, the range in evening readings. The vertical scale at the left indicates the number of subjects.

The standard deviation from the mean of all morning readings was 12.27 ± 0.34 mm. and of all evening readings, 10.47 ± 0.30 mm. The difference is 1.80 ± 0.45 mm. with the morning deviation the greater.

10. Addis, T.: Blood Pressure and Pulse Rate Levels; the Levels Under Basal and Daytime Conditions, Arch. Int. Med. **29**:539 (April) 1922.

The mean of the standard deviations in the individual cases was 5.57 ± 0.167 mm. for the morning series and 5.86 ± 0.21 mm. for the evening series, a difference of 0.29 ± 0.27 mm. These comparisons indicate that in the group as a whole, the morning readings show a slightly greater variability from the group mean than do the evening readings, but that the average variability in individual subjects is practically the same for morning and evening. In other words, the day's activity tends to bring the blood pressure of the group closer together, but has no appreciable effect on the individual variability.

The average range of systolic blood pressure over the period of six days was 16.29 ± 0.486 mm. in the morning and 17.86 ± 0.616 mm. in the evening, again indicating that, although the readings were somewhat lower in the morning, the variability in the morning is practically as great as the evening.

The difference between morning and evening readings was computed for each day and the average of these differences, without regard to sign, for six daily examinations was called the "mean difference" for the case. This mean difference, of course, does not indicate whether the morning or evening pressure was higher. The average mean difference for the 100 cases was 12.69 ± 0.42 mm.; the modal mean difference, 13.5 mm., the median, 12 mm. It appears that the average difference between morning and evening pressure is less than the average range over a period of six days in either the morning or in the evening.

Although the mean of all evening readings was 9.43 ± 0.44 mm. higher than the mean of all morning readings, yet in the 100 cases the morning average was higher than the evening average in fifteen cases and the same as the evening average in one case. With the readings taken morning and evening for six days on each of the 100 cases there were approximately 600 "pressure days." Of these, the morning readings were higher in 135 and the evening readings higher in 445; the two were identical in twenty.

Total Variation.—The mean of all readings, without regard to time, was 119.76 ± 0.244 mm. (differing slightly from the mean of the means of individual subjects, 119.15 ± 0.47 mm., because, in a few instances, five instead of six evening readings were taken, due to the absence of students from the house), with a standard deviation from the mean of 12.28 ± 0.17 mm. The mean of all the readings in each case, morning and evening, was computed and the standard deviation from this mean was considered the "standard deviation of the total readings." The mean of all these "standard deviation of the total readings" in individual cases was 8.67 ± 0.20 mm.; the mode, 7 mm., and the median, 9 mm. The total range of a subject is the difference between the lowest and the highest of the twelve readings, irrespective of whether they were taken in the morning or in the evening. The mean of these "total ranges"

was 27.47 ± 0.87 mm.; the mode, 26 mm., and the median, 26 mm. This mean total range is surprisingly high, in view of the mean morning range of 16.29 ± 0.489 mm. and the mean evening range of 17.86 ± 0.616 mm.

RELATION OF VARIABILITY TO MEAN PRESSURE

It has frequently been suggested by writers on the subject of blood pressure that repeated transient elevations of blood pressure probably

The Distribution of Mean Pressures and Case Standard Deviations in Individual Subjects

Mean Pressure	Standard Deviations: 0 to 0.9	1 to 1.9	2 to 2.9	3 to 3.9	4 to 4.9	5 to 5.9	6 to 6.9	7 to 7.9	8 to 8.9	9 to 9.9	10 to 10.9	11 to 11.9	12 to 12.9	13 to 13.9	14 to 14.9	15 to 15.9	16 to 16.9	Total
1. Morning Readings																		
90- 94	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
95- 99	..	1	2	..	2	..	1	..	..	..	..	..	..	..	..	..	..	6
100-104	..	..	1	..	4	1	..	..	..	2	..	..	..	..	..	..	..	8
105-109	..	..	3	1	4	4	2	..	..	..	1	1	1	..	..	..	..	17
110-114	..	..	4	2	2	3	4	3	4	1	..	..	..	..	..	..	1	26
115-119	..	..	..	2	3	2	2	1	1	..	..	..	..	..	..	..	..	11
120-124	..	..	..	1	3	1	2	3	1	1	..	..	..	..	..	..	..	12
125-129	..	..	2	1	1	1	1	2	1	..	..	..	..	..	..	..	..	9
130-134	..	..	..	..	1	1	..	2	2	..	..	..	..	..	..	..	..	6
135-139	..	..	..	1	..	1	..	..	..	..	..	..	..	..	..	..	..	2
140-144	..	..	..	..	1	..	1	..	..	..	..	..	..	..	..	..	..	2
Total	0	1	13	8	21	14	13	13	9	4	1	1	1	0	0	0	1	100
2. Evening Readings																		
105-109	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	1
110-114	..	..	2	2	1	1	..	..	2	..	..	..	..	..	..	..	..	8
115-119	1	1	3	1	..	4	5	3	1	2	1	..	1	..	..	..	..	23
120-124	1	1	3	6	5	2	2	3	3	1	..	1	..	1	..	1	..	30
125-129	1	1	..	2	1	3	1	4	2	2	..	..	..	..	..	..	..	17
130-134	..	1	1	1	1	3	1	..	1	1	..	..	..	1	..	..	..	11
135-139	..	..	1	..	..	1	2	..	..	1	..	..	..	..	..	..	..	5
140-144	..	..	..	..	1	1	1	1	..	1	..	..	..	..	..	..	..	5
Total	3	4	10	12	9	15	12	11	9	9	1	1	1	2	0	1	0	100
3. All Readings																		
105-109	..	..	..	..	..	..	2	..	1	3	1	..	..	..	..	..	..	7
110-114	..	..	..	..	3	..	2	2	5	5	1	2	2	1	1	2	..	26
115-119	..	..	..	..	1	3	2	10	1	6	4	2	2	1	..	..	..	32
120-124	..	..	..	..	1	..	1	1	1	2	2	..	..	..	..	1	..	9
125-129	..	..	..	2	..	3	1	2	2	2	..	..	..	..	..	..	..	12
130-134	..	..	1	..	..	..	..	2	..	..	1	..	..	..	1	1	..	6
135-139	..	..	..	..	1	..	2	1	2	1	..	..	..	..	..	..	..	7
140-145	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	1
Total	0	0	1	2	6	7	10	18	12	19	9	4	4	2	2	4	0	100

represent the first stage of a persistent hypertension.[11] If this is true one would expect a person's mean blood pressure to increase more or less in proportion to the increase in variability. In this study the mean

11. O'Hare, J. P., and Walker, W. G.: Arteriosclerosis and Hypertension, Arch. Int. Med. **33**:343 (March) 1924. Von Monakow, P.: Blutdrucksteigerung und Niere, Deutsches Arch. f. klin. Med. **133**:129 (Aug.) 1920. Lord Dawson of Penn: Discussion of Hyperpiesis, Proc. Roy. Soc. Med. **19**:27 (Jan. 25) 1926. Herrick, W. W.: Examination of the Circulatory System; the Importance of High Blood Pressure, Internat. J. Med. & Surg. **39**:507 (Dec.) 1926.

pressure in each case is computed for a series of from ten to twelve readings, and the variability in each case in this series is measured by the standard deviation of the case. A test of the relationship of these two factors was made by calculating the coefficients of correlation.

Chart 3 shows the distribution from which these correlation coefficients were computed. For the morning readings of blood pressure the correlation coefficient between the height of the pressure and its standard deviation was 0.126 ± 0.066; for the evening readings, the correlation coefficient was 0.049 ± 0.067; and for all readings taken in the case, irrespective of time, the correlation coefficient was -0.204 ± 0.065. One can conclude, therefore, that for the morning readings there is no signifi-

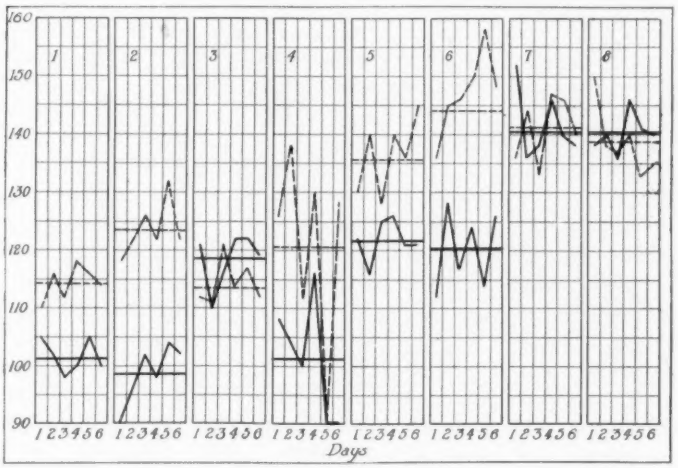

Chart 3.—The variation in blood pressure in morning and evening readings on eight subjects, during a period of six days. The solid line represents the readings taken in the morning; the broken lines, those taken in the evening. The vertical scale at the left indicates millimeters of blood pressure.

cant correlation between the height of the pressure and its variability; that for the afternoon readings the probable error of the correlation coefficient is even larger than the coefficient itself, allowing no possible correlation; and that for all the readings on the subject there is a negative correlation coefficient which is approximately three times as large as its probable error. In other words, the tendency exhibited is toward a slight negative correlation between the height of the pressure and its variability, that is, as the blood pressure increases the variability decreases. The significance of the difference,

however, is not sufficiently marked to justify any generalizations on the subject.

BLOOD PRESSURE CURVES OF REPRESENTATIVE CASES

In cases 1 and 2 (chart 3), the morning and evening pressure curves run almost parallel, with the evening pressures constantly higher. In case 3, the mean morning pressure is 4 mm. higher than the mean evening pressure, although on two days the evening pressure is the higher and the variation from day to day is not great. Case 4 shows a great variation from day to day in both morning and evening pressures. In case 5 the evening pressure rises, on one occasion, to 145 mm. and the mean evening pressure is 135.57 mm., while the morning pressure varies from 116 to 126 mm. with a mean morning pressure of 121.83 mm. Case 6 presents a morning curve which would be considered normal, but an evening curve that might justifiably be called hypertension. Cases 7 and 8 show persistently high pressures with relatively little daily variation. Although in case 7 the mean evening pressure is the higher and in case 8 the mean morning pressure is the higher, in neither case is there much difference between the morning and the evening mean.

COMMENT

Brooks and Carroll,[5] Luisada,[8] MacWilliam[12] and others have pointed out that there tends to be somewhat of a daily cycle in blood pressure with the highest pressure occurring in the late afternoon and the lowest pressure occurring in the latter part of the night. The present study shows that in 100 apparently normal young adults this increase which occurs during the day's activities approximates 9.5 mm. Proof that this increase is gradual throughout the day will require further observations.

With the distribution curves for standard deviation and for range as regular as they are, it is probable that similar variations will be found in other groups of subjects and that some daily variation of this kind is "normal." Further weight is given to the suggestion that more or less variability is normal by the fact that there is no positive correlation between the mean height of a person's blood pressure and its variability. This same lack of correlation throws grave doubt on the suggestion frequently found in the literature that transient elevations of blood pressure in young persons represent the beginnings of a persistent hypertension in later life. Of course, there was no evidence that this group of students contained any potential or early true hypertensions. How-

12. MacWilliam, J. A.: Blood Pressure and Heart Action in Sleep and Dreams, Brit. M. J. **2**:1196 (Dec. 22) 1923.

ever, since Bell and Clawson [13] pointed out that, as a conservative estimate, 15 per cent of persons more than 50 years of age will die from hypertension (Fahr [14] gave 23 per cent), it is exceedingly unlikely that this group of 100 unselected young men should not contain approximately a proportionate number of them.

Since this group, although unselected, includes a few persons who in this series of readings had a persistently high blood pressure, a question might arise in the minds of some readers as to whether or not this fact makes the group sufficiently abnormal to influence the data. However, as no positive correlation between the height of the blood pressure and the variability has been found, it can be said safely that the chance inclusion of these subjects did not in any way increase the variability found in the group as a whole.

SUMMARY

1. Readings of the blood pressure of 100 male university students were made in the morning and evening of six consecutive days.

2. The group was unselected and apparently of average height, weight and blood pressure.

3. The mean morning pressure of all readings taken was 114.94 ± 0.34 mm., and the mean of all evening readings was 124.37 ± 0.29 mm.

4. The standard deviation, which is the best measure of variability, was calculated for the morning readings and for the evening readings of each subject. For the 100 cases, the mean of the morning standard deviations was 5.57 ± 0.167 mm., and of the evening standard deviations was 5.86 ± 0.21 mm.

5. The variation in blood pressure from day to day as measured by standard deviation and range is practically the same in the series of morning readings as in the series of evening readings.

6. With an average morning blood pressure range of 16.29 ± 0.486 mm., an average evening range of 17.86 ± 0.616 mm. and an average total range of 29.47 ± 0.87 mm., it would seem that in any consideration of individual blood pressure readings the possibility of at least as much "normal" variation as this would have to be considered.

7. Study of the individual cases shows that in some subjects the difference between morning and evening pressures is consistently great enough for the one to be considered normal and the other hypertension,

13. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension, Arch. Path. **5**:939 (June) 1928.

14. Fahr, G. E.: Hypertension Heart, Am. J. M. Sc. **175**:453 (April) 1928.

and that in other cases the variation from day to day in the same person is sufficiently great for the pressure to be considered normal on one day and as hypertension on a subsequent day.

8. A positive correlation was not found between the height of the blood pressure and its variability. This fact makes it seem unlikely that transient elevations of blood pressure in young persons represent the first stages of a persistent hypertension.

PEPTIC ULCER

A STUDY OF FIVE HUNDRED AND FIFTY-SIX CASES *

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The past twenty years have witnessed a considerable advance in the knowledge of peptic ulcer. Credit for this is due chiefly to roentgenologists, who not only have simplified the diagnosis but have led to a better understanding of the pathologic physiology and complications of the disease. Therapy, especially surgical measures, likewise has improved. Diagnosis is made earlier, and most of the end-stages which occur when the ulcer is allowed to run its course are avoided. Yet the fundamental facts concerning peptic ulcer still are shrouded in mystery. There is much difference of opinion concerning the etiology, the cause and the nature of the symptoms. As long as this is so, there can be no unanimity of opinion regarding treatment.

Much of the disagreement on therapy depends also on the meager amount of statistical information in the voluminous literature on peptic ulcer. Many papers deal with the effect of a single form of treatment, often in a small number of cases, and usually with a short period of observation after the completion of the treatment. Evidence is scanty, and the conclusions are controvertible. Data are needed on a large series of carefully studied cases observed for a considerable period.

This paper deals with an analysis of the cases of patients with gastric and duodenal ulcer who have been admitted to the Peter Bent Brigham Hospital from its opening in 1913 to September, 1926. All cases in which the patients were admitted to the medical service have been included. Through the courtesy of Dr. Harvey Cushing and the other members of the surgical service, all surgical cases are included, with the exception of those of one member of the surgical staff who had already planned to report his own cases. A few cases, approximately twenty-five, which are recorded as cases of peptic ulcer in the hospital records have been omitted because the symptoms and the roentgen observations were such as to raise a reasonable doubt as to the accuracy of the diagnosis.

With these omissions, the series consists of 556 cases; 407 patients were admitted to the medical wards, 149 directly to the surgical and 155 were transferred from the medical to the surgical wards for operation.

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* From the Medical Clinic of the Peter Bent Brigham Hospital.
* Read in part before the Harvard Medical Society, Feb. 14, 1928.

A follow-up has been obtained on 460 patients (82.5 per cent). Seventy-six (13.6 per cent) of the total number are dead, from various causes; 264 (47.4 per cent) have been followed from their discharge to the present time; 120 (21.5 per cent) have been heard from at some time since discharge, but not recently, and ninety-six (17.5 per cent) have not reported. All patients were asked to return for a personal interview and examination, and an x-ray picture of the stomach. Those

TABLE 1.—*The Incidence of Gastric and Duodenal Ulcers as Reported by Other Observers*

Authority	Source	Location of Ulcer	Number of Cases	Percentage with Ulcer
Brinton, W.: Ulcer of the Stomach, London, J. & A. Churchill, 1857	Autopsy	"Peptic"	?	5
Howard, C. P.: M. News, Philadelphia, 1904, vol. 85, p. 673	Autopsy	Gastric and duodenal	10,841	1.32
Dietrich, H. A.: München. med. Wehnschr. **59**: 683, 1912	Autopsy	Gastric and duodenal	8,543	1.5
Ophüls, W.: A Statistical Survey of 3,000 Autopsies, Stanford Univ. Press, 1926, p. 268	Autopsy	Gastric and duodenal	3,000	2.2
Sturtevant, M., and Shapiro, L. L.: Arch. Int. Med. **38**: 41 (July) 1926	Autopsy	Gastric and duodenal	7,700	2.06
Lehman, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**: 185, 1926	Autopsy	Gastric and duodenal	1,000	20.2
Von Leube, quoted by von Ziemssen, Cyclopedia of Practice of Medicine, New York 1874, p. 195	Autopsy	Gastric	13,005	4.8
Fenwick, S., and Fenwick, W. S.: Ulcer of the Stomach and Duodenum, Philadelphia, P. Blakiston's Son & Company, 1900	Autopsy	Gastric	47,912	4.2
Martin, C. F., in Osler, W. and McCrae, T.: System of Medicine, ed. I, Philadelphia, Lea & Febiger, 1908, vol. 5, p. 176	Autopsy	Gastric	50,450	4.4
Hemmeter, J. C.: Diseases of the Stomach, Philadelphia, P. Blakiston's Son & Company, 1897, p. 495	Autopsy	Gastric	11,888	1.4
Sturtevant, M., and Shapiro, L. L.: Arch. Int. Med. **38**: 41 (July) 1926	Autopsy	Gastric	7,700	1.558
Martin C. F., in Osler, W., and McCrae, T.: System of Medicine, ed. I, Philadelphia, Lea & Febiger, 1908, vol. 5, p. 176	Autopsy	Duodenal	78,000	0.297
Fenwick, S., and Fenwick, W. S.: Ulcer of the Stomach and Duodenum, Philadelphia, P. Blakiston's Son & Company, 1900	Autopsy	Duodenal	13,055	0.26
Cooley, E. D.: Illinois M. J. **23**: 187, 1913.	Autopsy	Duodenal	38,106	0.41
Sturtevant, M., and Shapiro, L. L.: Arch. Int. Med. **38**: 41 (July) 1926	Autopsy	Duodenal	7,700	0.57
Martin, C. F., in Osler W., and McCrae, T.: System of Medicine, ed. I, Philadelphia, Lea & Febiger, 1908, vol. 5, p. 176	Clinical	Gastric	339,575	0.894
Howard, C. P.: M. News, Philadelphia, 1904, vol. 85, p. 673	Clinical	Gastric	161,599	0.57
Lynch, R.: Canad. M. A. J. **17**: 677, 1927....	Clinical	Peptic	944	1.45

who could not return to the hospital were reached by a letter, either directly or through their local physician or relatives. The duration of observation varied from six months to thirteen years, the average being slightly more than four years.

INCIDENCE

The number of patients with ulcer entering the medical service was 1.86 per cent of the total number of admissions to this service. This agrees fairly well with the incidence of ulcer as given by other observers, of which a few of the most representative figures are given in table 1.

With the exception of Brinton's 5 per cent and Lehmann's 20.2 per cent, there is little variation in the incidence of peptic ulcer. Post-mortem statistics for ulcer of the stomach apparently fall into two groups, those collected chiefly from sources from the continent (von Leube, the Fenwicks and Martin) and those from American sources (Hemmeter, and Sturtevant and Shapiro); the former averaging three times as much as the latter. The older papers show the clinical diagnosis of ulcer to be less common than the pathologic, but this has not been the experience at the Peter Bent Brigham Hospital. Present clinical observations differ also from the older pathologic reports in the relative incidence of gastric and duodenal ulcers. Whereas gastric ulcer used to be reported as more common than duodenal, the reverse is generally true today.[1] In this series there are 398 (71 per cent) cases of duodenal ulcer and 135 (24 per cent) cases of gastric ulcers.

Bolton [2] has quoted figures which suggest that there may be a wide variation in the regional distribution of ulcer. In an attempt to gain some information on this point, we have compared the relative incidence of the birthplaces of the patients in our series with those of all the patients admitted to the hospital. The close agreement between the two suggests that there is no racial difference in the susceptibility to peptic ulcer, unless it be somewhat higher among the Russian Jews.

Four hundred and five (72.8 per cent) of the patients were males and 151 (27.2 per cent) females. Of the patients with gastric ulcers, eighty-three were men and fifty-two were women; and of those with duodenal ulcer, 307 were men and ninety-one were women. Duodenal ulcers are generally regarded as occurring much more frequently in men,[3] but there is a conflict of opinion concerning gastric ulcers.[4]

Bolton[2] concluded that there was no sex difference.

In 1.8 per cent of our cases the patients had coexistent gastric and duodenal ulcers. Higher figures are given by Judd and Proctor [5] (16 per cent) and Perry and Shaw [6] (12.5 per cent).

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1. Lynch, R.: Canad. M. A. J. **17**:677, 1927. Eggleston, E. L.: Critical Review of 500 Cases of Gastric and Duodenal Ulcer, J. A. M. A. **75**:1542 (Dec. 4) 1920. Mayo, W. J.: Gastric Ulcer, ibid. **65**:1069 (Sept. 25) 1915.

2. Bolton, C.: Ulcer of the Stomach, London, E. Arnold, 1913.

3. Martin, C. F., in Osler, W., and McCrae, T.: System of Medicine, ed. 1, Philadelphia, Lea & Febiger, 1908, vol. 5, p. 176. Lynch (footnote 1, first reference).

4. Riegel, F., in Nothnagel: Encyclopedia of Practical Medicine, Diseases of the Stomach, Am. ed., Philadelphia, W. B. Saunders Company, 1903.

5. Proctor, O. S.: Surg. Gynec. Obst. **41**:63, 1925. Judd, E. S., and Proctor, O. S.: M. J. & Rec. **121**:93 (Jan.) 1925.

6. Perry, E. C., and Shaw, L. E.: Guy's Hosp. Rep. **50**:171, 1893.

AGE

The average age at which symptoms of ulcer were first noticed was 36.8 years (35.9 for males and 37.8 for females). The youngest patient was 6 years old, and the oldest was 80. Sixty-four and seven-tenths per cent of the cases occurred before the patients were 40.

Chart 1 shows the age at onset in five-year periods for both sexes. The curve is nearly symmetrical and is similar in appearance to those given by Ophüls,[7] Riegel [4] and Martin.[3] It would seem that ulcer as a disease of young adults has been stressed too much.

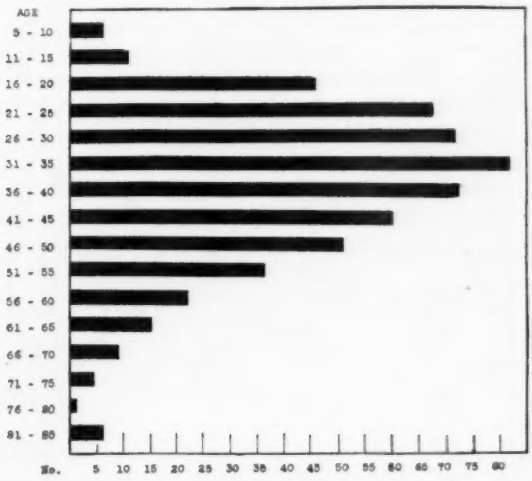

Chart 1.—Age at onset of symptoms of ulcer.

The question arises whether, in spite of the symmetrical curves which all obtain, the incidence of ulcer during the later years of life is not actually higher because the number of people in these age groups is less than in the earlier ones. This would seem to be answered in the negative by Ophüls,[7] who showed that the ratios of the cases in each age group remain rather constant after the third decade, from 2.2 to 3.2 per cent.

In 3 per cent of our series, symptoms of ulcers began before the patients were 15 years of age, and in 11.3 per cent before they were 20. Proctor [8] found an even greater incidence in childhood (4.2 per cent in his 2,000 cases).

7. Ophüls, W.: A Statistical Survey of 3,000 Autopsies, Stanford University, Stanford Univ. Press, 1926, p. 268.

8. Proctor (footnote 5, first reference).

OCCUPATION

The occupation of the patient has frequently been proposed as a factor in the etiology of peptic ulcer, although most students of the subject have been unable to find any connection between the two. This is equally true in this series in which the list of occupations numbered more than fifty and are not of related types. Since physical exertion also has been postulated as an etiologic factor, an attempt was made to classify all the cases according to the degree of muscular activity which the occupation of the patient entailed. Among persons in sedentary occupations (professional and executive men, office and clerical workers), ulcer occurred in 198; and of those in moderate occupations (skilled labor, factory workers, house workers, store keepers, etc.), in 235; and among those in strenuous occupations (unskilled labor, engineers, etc.), in 123. We do not have any figures as to the ratio of these occupations in the general hospital population, but have the impression that they are not far different, and that there is no connection between ulcer and exertion.

FAMILY AND PAST HISTORY

There were only nine families in which peptic ulcer was known to exist, four members having died of it. In addition, there was a history of stomach trouble in thirty-seven which was fatal in nineteen cases. These figures do not suggest an hereditary tendency for ulcer, although Hurst [9] stated that he had seen it run in a few families, and Draper [10] was inclined to be more positive, describing a definite constitutional type for ulcer.

Thirty (5 per cent) of the patients had hypertension, and thirty-five (6 per cent) had generalized arteriosclerosis, an incidence no greater than would be expected in other persons (at the age periods). Smithies [11] found 14.7 per cent of his cases of gastric ulcer with these complications, but this seems too small a figure to warrant the assumption that they play any determining factor in ulcer, as has been claimed by Virchow [12] and later by Ophüls.[7] No other disease occurred frequently enough in the past history to suggest an association with ulcer.

SYMPTOMATOLOGY

Duration and Periodicity.—The average duration of symptoms at the time of entry was seven years. In many patients, of course, symptoms

9. Hurst, A. F.: Brit. M. J. **1**:559, 1920.

10. Seegal, D.; Draper, G., and Dunn, H. L.: Human Constitution: Clinical Anthropometry, J. A. M. A. **82**:431 (Feb. 9) 1924.

11. Smithies, F.: Am. J. M. Sc. **166**:781, 1923.

12. Virchow, R.: Virchows Arch. f. path. Anat. **5**:362, 1853. Wilson, C. B., and McDowell, I. E., Am. J. M. Sc. **13**:208, 1914.

had existed for only a few days or months; in ninety-seven for less than a year. On the other hand, 63 per cent had had symptoms for more than two years, and in many the duration of the symptoms extended into decades. Six patients had had symptoms for from thirty-six to forty years. In cases of short duration a diagnosis frequently had not been made, but in many of long duration the cause had been recognized and the condition treated.

Almost all of the patients had experienced periods of relief from symptoms, which occurred as frequently without medical intervention as with treatment. The remissions were from a few months to a year in duration and usually exceeded the relapses. In a few patients there was a remission of ten years and in one of twenty years.

Five hundred and thirty-nine patients of the total 556 had some form of abdominal distress. Seventeen, or 3 per cent, had none, the ulcers being found post mortem or by roentgen examination. This is somewhat less than was formerly taught, namely, that in about 10 per cent of the cases of gastric ulcer and 20 per cent of those of duodenal ulcer the condition is symptomless.

One hundred and fifteen (20.6 per cent) of the patients who had distress said that it was slight; 322 (58 per cent), that it was moderate, and 102 (18.4 per cent), that it was intense.

In the great majority of patients (461) the pain was in the upper part of the abdomen. Those who had the most typical histories of ulcer placed it in the epigastrium, and those whose symptoms were more indefinite tended to name other regions.

The pain originated in the right lower quadrant in seven, and radiated there in five others. This is interesting in view of the increasing evidence of a physiologic relationship between the pylorus and the ileocecal region, and because a few patients enter the hospital every year who have had appendectomies done because of symptoms which are later shown to be due to peptic ulcer.

The pain was typically boring, grinding, gnawing or burning in only a few (136). Frequently it was not characterized except as "pain." In 282 there was a sense of fulness or distention in the abdomen, occasionally as the only distress, but often associated with belching. "Gas" was also one of the commonest symptoms, occurring in 392 cases; but its significance is difficult to estimate, for it occurs so frequently without ulcer. Its frequency in this series suggests that intestinal disturbances of a functional nature were also present.

Radiation of the pain occurred in approximately 104 cases. The most frequent site for the referred pain was the back (fifty-one). Five patients had pain referred to the right shoulder; three had cholelithiasis and one a subdiaphragmatic abscess, which probably explains the radia-

tion. Three of the eleven patients in whom the pain spread to the right upper quadrant had a pathologic condition of the gallbladder in addition to the ulcers. Radiation occurred in various directions in thirty-two other cases for which no explanation other than ulcer could be found.

Three hundred and eight placed the onset of their distress in definite relation to meals, and in 252 of these it occurred from one to three hours afterward. There was no apparent difference in behavior between gastric and duodenal ulcers.

Three hundred and eighty-five patients noted relief from pain after taking food, and 394 after taking sodium bicarbonate. Forty-eight were relieved by the application of pressure or heat to the epigastrium. One hundred and forty-two were relieved by vomiting, and 140 noticed some relief after belching.

Why there is such a wide variance in the amount of pain which patients with peptic ulcer experience is not understood clearly. There is no sex difference according to our records, which also do not disclose any association with the duration of symptoms of ulcer or the age of onset. It is more probable that the emotional constitution of the person and his susceptibility to pain stimuli determine how bitterly he complains. This is strikingly true in many cases; yet there are other patients who, most phlegmatic in all other respects, suffer extreme pain from the ulcers, regardless of the type. Unfortunately, it has been impossible to analyze our hospital cases from this standpoint.

Nausea and Vomiting.—A considerable number of patients had nausea (196) or vomiting (356) during the periods when the ulcers were giving pain. In most cases the cause of these symptoms was not evident, although apparently they were due to a large retention in thirty-five cases. Occasionally it seemed, in observing individual cases, that the vomiting was the result of the severity of the pain that the patient experienced; yet this could not account, at most, for more than seventy-six. Riegel [4] described a case in which vomiting was the outstanding symptom. Twenty-five cases in this series might be so classified.

Condition of the Bowels.—Constipation was a symptom in 290 patients. A few were constipated only during their attacks of ulcer pain. Six had diarrhea at this time, and four were troubled with alternating constipation and diarrhea. Such associated disturbances of the bowels suggests that an ulcer in some instances may disturb the whole intestinal tract.

Weight.—One hundred and twenty patients of the cases in which weight was mentioned lost during their attacks of ulcer distress, the loss varying from 5 to 50 pounds (2.3 to 22.7 Kg.). Only five gained weight during their illness. In the other 168 cases, a change in weight did not occur.

LABORATORY DATA

White blood cell counts were made in all but fourteen cases. One hundred and sixty-eight patients had a leukocytosis (over 10,000). In twenty-five cases perforation had occurred. The condition in three cases was due to a complicating disease such as pneumonia. Sixty-six were patients who had bled and showed the mild increase associated with secondary anemia. In seventy-four cases, however, there was nothing to account for the leukocytosis. It seems important to bear this in mind, since the observation of an abnormal white count in an otherwise simple case of ulcer sometimes causes undue apprehension. Red blood cell counts, as well as the examinations of the stools, were of interest only

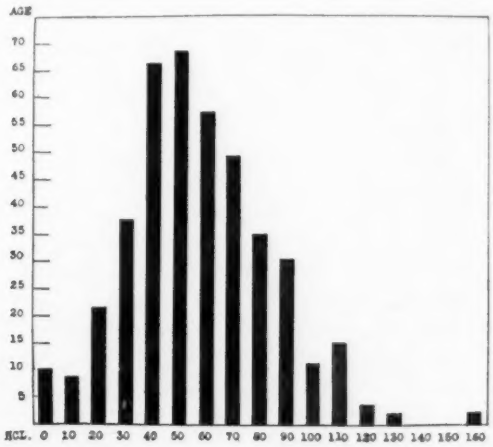

Chart 2.—The highest values of free hydrochloric acid in the gastric analyses of 414 cases of peptic ulcer.

in relation to hemorrhage and are taken up under that heading. The blood pressure and urine were of no significance unless they gave definite evidence of arterial or renal disease.

Gastric acidity in cases of ulcer is of interest in view of the different opinions held concerning its importance in diagnosis, the causation of pain and its effect on healing. A gastric analysis was done on 414 patients. A test meal of 60 Gm. of white bread and 200 cc. of water was given, and the contents removed fractionally with the Rehfuss tube, or completely at the end of an hour with the Ewald tube. The highest value of free hydrochloric acid has been recorded in terms of the number of cubic centimeters of tenth normal sodium hydroxide necessary to neutralize 100 cc. of gastric contents, as shown in chart 2.

Values were recorded on patients from 0 to 150. Approximately 50 per cent of the patients had a free acidity of fifty points or more, and 25 per cent of the total had a free acidity of seventy or over. The majority of the patients, therefore, may be said to have a hyperacidity. On the other hand, one fourth of all the patients had a normal range of from twenty to forty points of free acid, and 9 per cent had twenty or less.

When the acid values vary so freely through such a wide range, the gastric analysis can be of little diagnostic value in the individual case. Moreover, the not infrequent custom of diagnosing the presence of an ulcer on the basis of an existing hyperacidity does not seem warranted, when the tendency for the ulcer to occur with hyperacidity is no greater than represented by this series.

There is a wide range of opinion among writers concerning the ability of ulcers to develop and persist in the absence of free acid, and concerning the possibility of an ulcer giving typical distress of ulcer in the absence of free acid.[13]

An analysis of the results for ten patients who were found to have no free hydrochloric acid in their gastric contents shows that the condition in one was in association with pernicious anemia, and doubtless a true achylia gastrica. This patient had never experienced distress from ulcer, and the characteristic deformity of duodenal ulcer was discovered in a routine roentgen examination. The evidence for absence of free acid in the other cases is unconvincing. Five of them had a high combined acid. Three others showed free hydrochloric acid when they were given a large meal, or when aspiration was done during a period of distress. In the last case, only one specimen of gastric juice was obtained, and a test for pepsin was not made. There is no proof, then, that true achylia gastrica occurred in any uncomplicated case in this series.

There are no data on these patients which show the relationship of acid to pain, since special work has not been done in this connection.

The usual amount of distress caused by the ulcer was compared with the highest acid values found in the patients' routine gastric analysis. Table 2 shows that about the same proportion of patients in each acid group had severe pain, and that in general the degree of distress was not related to the degree of acidity. This is in agreement with the work of Carlson[14] and Bolton.[2] It is true that in cases in which nocturnal

13. Eggleston (footnote 1, second reference). Bolton (footnote 2). Moynihan, B.: Brit. M. J. **1**:221, 1923. Carlson, A. J.: Am. J. Physiol. **45**:81, 1917. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomach, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch. Int. Med. **29**:11 (Jan.) 1922.

14. Carlson (footnote 13, fourth reference).

distress occurred, the acid values were a trifle higher than for all the cases, but this was so slight as to be without significance, averaging fifty-one for all cases and fifty-five and nine-tenths for those with nocturnal distress. Pain at night in this condition, however, may be dependent on a continuous night secretion.

To what extent does the degree of acidity influence the healing of an ulcer? This answer could be reached best by following a series of cases from the onset of symptoms throughout life. Although this is rarely possible, some idea should be gained by comparing the acid values

TABLE 2.—*A Comparison of the Amount of Pain with the Free Acid in the Gastric Analysis of 414 Cases of Peptic Ulcer*

Highest Values of Hydrochloric Acid in Gastric Analysis	Percentage			
	None	Slight	Moderate	Severe
0	7	26	59	8
0 - 10	0	17	61	22
11 - 20	0	40	45	15
21 - 30	0	35	50	15
31 - 40	2	18	63	17
41 - 50	7	15	67	11
51 - 60	0	16	70	14
61 - 70	3	13	63	21
71 - 80	0	19	60	21
81 - 90	8	21	50	21
91 -100	0	41	41	18
101 -110	0	16	68	16
110 -120	0	0	60	40

TABLE 3.—*A Comparison of the Gastric Analyses of Patients with Ulcer Having Symptoms of Less Than One Year with Patients with Ulcer Having Symptoms for Twenty Years or More*

Acid Values	Less Than 1 Year	More Than 20 Years
0 - 10	0	2
11 - 20	2	1
21 - 30	3	7
31 - 40	10	5
41 - 50	6	3
51 - 60	6	10
61 - 70	4	3
71 - 80	1	2
81 - 90	4	1
91 -100	1	1
101 -110	1	3

in long-standing cases of ulcer with the acidity in cases of recent origin. There were thirty-eight cases with symptoms for twenty years or more, and these were compared with an equal number of cases with symptoms of less than one year (table 3). No essential difference occurred in the acidity of the two groups.

ROENTGEN EXAMINATIONS

X-ray studies were made in 510 cases in our series, and definite ulcers were shown in 474 (93 per cent). X-ray pictures failed to show the ulcer in thirty-six cases (7 per cent); eighteen of the latter were shown to have an ulcer at operation; six, in addition to typical symptoms,

had had one or more hemorrhages, and the diagnosis in twelve was based on the history and reaction to treatment alone. Sixteen of the patients were seen before 1919, in the developmental period of the radiographic signs of ulcer, and one would expect more cases to be missed then than now. In the hands of a skilled roentgenologist, a definite diagnosis of ulcer can be relied on. A negative roentgen examination with a good history is probably not of so much value, for an ulcer may be so situated that it cannot be demonstrated.

COMPLICATIONS

Hemorrhage.—Riegel [4] reported that one third of all patients with ulcer suffer from gross hemorrhage according to the statistics of different observers, and he felt that this proportion would be even higher if all the blood lost in the stools could be known. Osler and McCrae [15] concluded, from various authorities, that hemorrhage occurred in from 25 to 60 per cent of all cases of gastric ulcer, with an average of 28 per cent, and in about 50 per cent of the cases of duodenal ulcer. Later writers found a smaller percentage. Thus, Mayo [16] reported that hemorrhage occurred in 17 per cent of cases of gastric ulcer and 15 per cent of the cases of duodenal ulcer; Eggleston [17] reported this condition in 19 per cent of his 500 cases. Our figures correspond with those of the older observers, for 194 (34.8 per cent) patients in this series had one or more gross hemorrhages. These do not include that unknown number of patients who have doubtless lost such small amounts of blood as to escape notice, and those in whom the ulcers were found to be oozing; if these were included, the percentage would be 40 or more.

The importance of this complication, both for the life of the patient and for the economic disability that it entails, has not been emphasized sufficiently in recent years. Its gravity is apparent when it is seen that eight patients died from loss of blood. This is 4.1 per cent of the cases in which hemorrhage occurred, and is 1.4 per cent of the series. Four patients died from a single hemorrhage and four after several of them.

Examination of the blood and stools showed that eighty of these patients were definitely anemic at the time of their entry into the hospital (fourteen had from 1,000,000 to 2,000,000 red blood cells per cubic millimeter; thirty-two had from 2,000,000 to 3,000,000, and thirty-four had from 3,000,000 to 4,000,000). Twenty-four patients who showed no evidence of anemia had typical tarry stools. Thirty-one others showed occult blood in the stools, without anemia. The remaining fifty-nine, at one time or another during the course of their disease, had a recog-

15. Osler, W., and McCrae, T.: System of Medicine, ed. 1, Philadelphia, Lea & Febiger, 1908, vol. 5.

16. Mayo (footnote 1, third reference).

17. Eggleston (footnote 1, second reference).

nizable gross hemorrhage, which, on entry, did not show any effect on the blood or feces. In addition, there were sixty patients who had never had a definite hemorrhage who showed microscopic blood in the stools.

Hemorrhage was the first indication of the presence of an ulcer in twenty-five cases. Seventy-three patients had a gross loss of blood within the first two years. The time at which the other patients bled was rather evenly distributed over a period of from two to twenty-five years, eleven patients having done so after twenty years. It appeared that after a rather high incidence in the first two years, the tendency for hemorrhage to occur dropped to about 23 per cent and remained there. The number of cases is too small, however, to justify a definite conclusion.

The patient's age at the time when symptoms of ulcer first develop seems to be related to the danger of hemorrhage.

Table 4 shows a steady increase in the tendency of ulcers to bleed as they develop in patients from youth to old age. An ulcer found in

TABLE 4.—*The Age of Onset of Symptoms of Ulcer as Compared with the Tendency to Hemorrhage*

Age in Decades	Number Cases with Hemorrhage	Percentage in Each Age Group of Series
10 - 20	1	1.5
21 - 30	31	22
31 - 40	60	39
41 - 50	45	41
51 - 60	39	67
61 - 70	14	63
71 - 80	4	80

a man 50 years of age should be looked on as more likely to bleed if recently acquired than if of long duration.

There was a greater proportion of males than females in the cases with hemorrhage; for 150 patients in the series were males, and forty-four were females. This is 37 per cent of the male group and 29 per cent of the female group. There was also a greater proportion of vascular disease in the cases in which hemorrhage occurred than in the whole series. Fifteen of the patients had hypertension, and seventeen had generalized arteriosclerosis. Approximately one half of the patients with a blood pressure of 160 or more have bled.

No other factors were found which were related to hemorrhage. The patient's customary degree of activity did not play any rôle. Seventy of the cases with hemorrhage occurred in persons who were in sedentary occupations, seventy-eight in those doing a moderate amount of work and forty-six in those doing strenuous physical work. The same values of free hydrochloric acid in the gastric contents occurred in these cases as in the whole group. The amount of pain experienced by these patients was not different from that in others who had not bled.

Recurring hemorrhages were frequent. Forty per cent of the patients that bled had more than one hemorrhage, and 15 per cent had "several" or "many." The patient in the most extreme case had one or more annually for twenty-five years. More than one half the patients had a second hemorrhage within a year after the first, which agrees with Riegel's [4] observations that a second hemorrhage usually occurs soon after the first; on the other hand, many had a second hemorrhage only after a lapse of several years.

Perforation.—Thirty-eight patients in the series (6.8 per cent) suffered acute perforation of the ulcer. This is in substantial agreement with the older writers (Fenwick,[18] 5.5 per cent; Martin,[3] 3.4 per cent).

Death occurred in eleven cases, or 28 per cent, but those who recovered did not experience any ill effects as far as their general condition was concerned. Thirty-one patients were males (7.6 per cent) and seven females (4.6 per cent). Why these ulcers perforated and the others did not is no more apparent than why certain ulcers bleed.

The age of the patient at the time of onset does not bear any apparent relation to perforation. An ulcer may perforate at either extreme of life (two perforated before the patients were 20 years of age and two after the patients were 60 years of age) but usually the perforations occur during the middle period when the disease is most common.

Approximately one fourth of the patients had experienced ulcer distress for only a short time before perforation occurred. These are the dramatic cases which contribute to the idea that young ulcers are more likely to rupture than older ones. Indeed, the reverse may be true; for as Brown [19] has pointed out, the absence of ulcer distress before perforation does not indicate that the ulcer is acute. In our experience, the cases of perforation were divided equally between the different age groups. Most patients do, in fact, have distress for a long time before perforation occurs; eight of the thirty-eight patients had had symptoms for more than ten years.

In seven of the cases in the series there was chronic perforation of the ulcer: four of them were gastric; one had broken through the posterior wall of the stomach and was walled off by the liver and omentum; one, on the lesser curvature, after causing an hour-glass deformity perforated into the duodenum; another, on the lesser curvature, had burrowed into the pancreas, and one had penetrated the liver. One duodenal

18. Fenwick, S., and Fenwick, W. S.: Ulcer of the Stomach and Duodenum, Philadelphia, P. Blakiston's Son & Company, 1900.

19. Brown, K. P.: Edinburgh M. J. **32**:207 (April) 1925.

ulcer was completely walled off by local adhesions, another by the gallbladder and the last had entered the pancreas and caused death by opening a large artery.

Cancer.—The incidence of ulcer as a forerunner of carcinoma is a subject of considerable discussion at present, and there has been much conflicting evidence brought forward.[20]

One hundred and twenty-nine of the 135 patients with gastric ulcer in this series have not shown any evidence of carcinoma to date. Eighty-eight of them were examined at operation or pathologically; the condition in the remainder was diagnosed only by history and roentgen observations. The average duration of symptoms was nine years, and the average follow-up in the 103 cases that were traced was four and a half years. For an average observation period of thirteen and a half years, therefore, carcinoma has not been detected in them. The remaining six cases were as follows:

One, a man, aged 51, who had been ill for one year, died of cancer of the stomach with extensive metastases one year after his hospitalization. Although the condition was diagnosed as ulcer at the time, later events make it probable that this was a case of cancer from the start. The second case was also doubtful. The patient was a woman with symptoms of ulcer extending over a period of twenty-five years, in whom the x-ray picture showed a gastric ulcer at the pylorus. Despite this fact, she was clinically thought to have cancer and, therefore, has been included at this point. Unfortunately, she refused an operation and attempts to follow her have not been successful.

A man, aged 58, who had been ill for four years, showed carcinomatous changes in the ulcer at operation, and died three years later of cancer. Similarly, a man, aged 46, who had been ill for two and a half years with a condition diagnosed as ulcer was found to have a suggestive lesion at operation; he died four months later of cancer with metastases. The fifth case was that of a woman, aged 65, who had had symptoms for ten years, and who at operation showed malignant changes in the edges of the ulcer. The last case was in a man, aged 46, with the same duration of symptoms, who at operation and by pathologic examination was reported to have a simple ulcer of the lesser curvature; yet he died of adenocarcinoma of the stomach four and a half years later without intervening relief from symptoms.

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20. Freeman, F. P., and Flinn, L.: Tr. Am. Gastro-Enterol. A., 1925, p. 20. Campo, G.: Siglo méd. 77:193 (March) 1926. Stewart, M. J.: Brit. M. J. **2**:882 (Nov.) 1925. Lawrence, J., and Bock, C.: Boston M. & S. J. **195**:651, 1926. Wilson, L. B., and MacCarty, W. C.: Am. J. M. Sc. **138**:846, 1909. MacCarty, W. C., and Broders, A. C.: Chronic Gastric Ulcer and Its Relation to Gastric Carcinoma, Arch. Int. Med. **13**:208 (Feb.) 1914.

Three of the patients may not have developed the cancer from ulcer. Assuming that they did, only 4.4 per cent of the patients with gastric ulcer to date are known to have shown evidence of a malignant condition.

In none of our patients with duodenal ulcer has the condition become malignant. This is a rare event, but occasionally has been reported.[21]

Retention.—In 135 cases (34 per cent) some delay was shown in the emptying time of the stomach. This was determined by roentgen examination six hours after a standard meal in 130, and clinically or by operation alone in five cases. Retention was apparently due to pyloric spasm in ninety-two. Some degree of organic obstruction was present in only forty-three cases; this was moderate in sixteen and marked in twenty-seven. In 24 per cent of the patients with duodenal ulcer, retention was produced, and in 17 per cent of those with gastric ulcer.

The development of obstruction seems to be an individual characteristic, for analysis of the cases revealed no constantly associated condition. Sex was found to be irrelevant. Eight and a half years was the average duration of symptoms of ulcer in these patients, but frequently they occurred much sooner. There was no association between obstruction and the amount of gastric acidity. The amount of pain experienced was comparable with that given by the entire group with ulcers. Thirty-eight of the forty-three patients with organic obstruction had vomited more or less frequently, but it was the outstanding symptom in only three.

The importance of retention in prognosis is hard to estimate. Patients with this symptom as a group did no better and no worse than the other patients. If retention is due to organic changes, the problem of course becomes one for surgery rather than for medicine.

Hour-Glass Deformity.—An hour-glass deformity occurred in sixteen cases as shown by the x-ray picture. Six of these were spasmodic, no deformity being found at operation. In all except two cases the ulcers were situated on the lesser curvature of the stomach; one of these was on the posterior wall of the stomach near the lesser curvature, and the other in the duodenum with an associated contracture of the stomach. In one of the thirteen patients who came to operation the ulcer appeared to be healed. The rest showed open craters surrounded by some infiltration, and three had become adherent to the pancreas. One had formed a fistulous communication with the

21. Ewald, C. A.: Berl. klin. Wchnschr. **32**:527, 1886. Eichhorst, H.: Ztschr. f. klin. Med. **14**:519, 1888. Boxwell: Lancet **2**:1687, 1907. Mayo, W. J.: Ulcer of the Duodenum, J. A. M. A. **51**:556 (Aug. 15) 1908. Letulle, M.: Bull. Soc. anat. de Paris **11**:741, 1897.

duodenum.[22] Eleven occurred in females and five in males. This observation agrees with the impression of others that hour-glass contraction occurs more frequently in females. All these patients experienced typical symptoms of ulcer although they were complicated by symptoms of obstruction. They complained of fulness or a lump after small amounts of food were taken. The sensations were intense in four, moderate in ten and mild in two. As a result, it was sometimes difficult to obtain a good history of relief from eating.

No good cause was found to explain the organic stricture. One patient had syphilis, but antisyphilitic therapy had no effect on the lesion. None showed malignant changes, and all have progressed fairly well. Fourteen have been followed for an average of five years; none has died, and most of the patients are in good condition.

ASSOCIATED DISEASES

Pulmonary Tuberculosis.—Thirty patients (5.4 per cent) had pulmonary tuberculosis, which was considered inactive in eighteen and moderately advanced in five; it was the cause of death in one. An active process did not seem to influence the course of the ulcer, nor was there any greater association of the two diseases than one would expect. This disagrees with some of the older writings.[23]

Syphilis.—The relation of syphilis to ulcer also has been stressed during the past, but there was no greater incidence in these cases than in the general admissions to the hospital. A Wassermann test was done on the blood of 433 patients and was positive in only 26 (6 per cent). Twelve of the patients had a duodenal ulcer, and five a gastric ulcer. One patient had marked obstruction from a duodenal ulcer and received only antisyphilitic treatment. At the end of two years all obstructive symptoms had disappeared, although typical ulcer distress was still present. This is the only case in which there was clinical evidence that syphilis influenced the ulcer. In addition, three of the patients were operated on, and no evidence of syphilis was found in the ulcer or stomach.

Foci of Infection.—There was no evidence that carious teeth, diseased tonsils or sinusitis occurred more frequently in this series of cases of ulcer than should be expected in any group of persons. One hundred and eighty were said to have bad teeth; forty-two had had tonsillectomies and twenty-five others had pathologic changes in the tonsils.

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22. Monroe, R. T.: Am. J. M. Sc. **174**:579 (Nov.) 1926.

23. Dreschfeld, J.: J. Allbutt and Rolleston System of Medicine, New York, The Macmillan Company, 1910, vol. 3, p. 446. Lisa, J. R.: Surg. Gynec. Obst. **41**: 664 (Nov.) 1925. Surmont, H.: Medicine **7**:772, 1926. Cade, A., and Ravault, P.: Am. J. M. Sc. **174**:579 (Nov.) 1926.

The condition of the gallbladder was noted in 228 cases, and was found to be normal when examined at operation for ulcer in 168 and by roentgen examination in twenty-nine. A diseased gallbladder was found in twenty-five cases at operation and in six, or 13 per cent, by cholecystograms.

The appendix was noted in eighty-nine cases. Thirty-five patients had had their appendix removed during an acute attack, but only twenty-five of these occurred after the onset of symptoms of ulcer. Eighteen had had appendectomies as a means of treatment for ulcers. Examination of thirty-five appendixes removed incidentally during an operation for ulcer revealed pathologic processes in only four.

DEATH

Seventy-six patients are dead; thirty-five died of causes not related to ulcer; twenty patients died from ulcers, if the six with gastric cancer are included; eight died of hemorrhage and six of perforation of the ulcer without operation. Twenty-one others died following an operation undertaken to cure the ulcers. This series, therefore, suffered a mortality from all causes of 13.6 per cent (or 7.2 per cent from ulcer).

RESULTS

The results of treatment have been observed in 460 cases which have been followed for periods varying from one half to thirteen years, the average being somewhat more than four.

Many of the patients had more than one kind of treatment (460 cases having received 562 courses of treatment), so that the average observation period for a particular form of therapy may be more or less than the general average. It is important to keep this in mind when considering results, particularly of medical as compared with surgical methods, for the average duration of follow-up in the medical cases is only two and one-half years, whereas in the cases requiring surgical measures it is slightly more than four. This difference is due to the fact that the great majority of patients who entered in the early period of the hospital's existence were operated on.

To obtain a satisfactory classification of results, a two-fold system was adopted. Depending on the evidence derived from careful questioning and examination, patients were divided into three groups, labeled "good," "improved" and "unimproved." Once the patient's group was determined, his attitude toward the treatment was classified as "satisfied" or "not satisfied."

Those were called "good" who, since treatment was concluded, have experienced no discomfort of any kind, either from the ulcer or from the treatment itself. While the latter requirement excludes a certain number that might be included by other investigators, it does not seem

logical to assert that a patient is entirely well in whom, during the process of becoming so, other symptoms than the original ones have been produced. In regard to what constitutes symptoms of ulcer there is, unfortunately, no complete agreement. We, therefore, have had to use our own judgment. Although a complete presentation of our views cannot be given here, it may be said that we do not agree with the idea that ulcers do not cause a specific group of symptoms. On the contrary, ulcers cause a distinct type of distress, but it may require much time and patience to separate it from other associated discomforts. A patient, therefore, having distress occurring at typical periods and relieved by food and alkali, was considered to have ulcer distress and was not classified as "good." No matter how mild this distress might be, it was sufficient to remove him from this class. In the few borderline cases, as it was known that an ulcer had been present, it seemed fairer to assume that the symptoms were due to ulcer than that they were not.

Patients in the "improved" group suffer at times from symptoms of ulcer, but, for one cause or another, are better for having been treated. In some, the symptoms are milder; in others, the remissions are definitely prolonged. In the surgical group a few patients are included in whom the obstruction has been relieved even though the symptoms are not affected, unless they are so severe as practically to incapacitate the patient. In the "unimproved" group are placed all patients who at the time of observation were obviously no better than before they underwent treatment.

After each patient had been thus classified, he was asked to express his satisfaction, or lack of it, with the results of treatment. If no definite answer was forthcoming, it was usually possible to obtain an adequate impression by his willingness to undergo similar treatment again with the hope of obtaining similar results. In the case of the few who did not return for a personal interview, it was estimated from the tone of their letters or those written by their relatives. As shown in table 5, the two forms of classification agreed extraordinarily well.

Table 5 shows the general results of treatment. There was only a little difference in the behavior of patients with gastric and those with duodenal ulcers, and, in order to simplify matters, they have been grouped together. The first column shows that as a result of treatments given to patients 37.8 per cent showed good results and the patients were satisfied, 40.6 per cent did not show any improvement and the patients were not satisfied and 21.6 per cent showed improvement. In other words, only 60 per cent were benefited by treatment of all sorts given over a thirteen year period.

In the next column are shown the results in forty-three patients in whom ulcers were not treated, and who, therefore, serve as a control

group. The reasons for lack of treatment are various; some patients refused it; some were in periods of remission, and it was not advised. The follow-up record shows that untreated patients acted in general about the same as treated patients; in 23.2 per cent results were good; in 25.6 per cent improvement was shown, and in 51.1 per cent of the patients the condition was unimproved. There were, thus, only 10.5 per cent fewer failures in those who were treated than in those who were not.

One hundred and eighty-six patients were treated by some form of medical regimen without a previous operation. In 29.8 per cent there were good results and the patients were satisfied; in 20 per cent there was improvement and the patients were satisfied; in 15 per cent there was improvement but the patients were not satisfied, and in 48.7 per cent there was no improvement and the patients were not satisfied.

TABLE 5.—*Results of Treatment of Patients with Ulcer*

Result	All Treatment		No Treatment		Medical* Treatment		Surgical† Treatment	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Good and satisfied	196	37.8	10	23.2	55	29.8	111	44.8
Improved and satisfied	85	16.3	11	25.6	37	20	23	9.2
Improved, not satisfied	28	5.3	..	....	4	1.5	14	5.6
Unimproved, not satisfied	210	40.6	22	51.1	90	48.7	100	40.6
Totals	519		43		186		248	

* Medical treatment in cases not having had operation before. The average observation period for medical cases was two years and five months.

† Excluding cases of perforation. The average observation period for surgical cases was four years and one month.

Two hundred and forty-eight patients were treated by surgical measures, excluding those in whom an acute perforation was present. Such a condition demands emergency methods and is not strictly comparable with operations performed under more favorable conditions. As a result of these measures, 44.8 per cent of the patients showed good results and were satisfied; 9.2 per cent showed improvement and were satisfied; 5.6 per cent showed improvement but were not satisfied, and 40.4 per cent did not show improvement and were not satisfied. Surgical measures have given complete relief to date to more patients than medicine, 44.6 as compared with 29.8 per cent. There were also fewer patients unimproved when surgical measures were used than when medicine was prescribed; 40.6 as compared with 48.7 per cent. These figures, however, cannot be compared too closely. As already pointed out, the average period of observation for the two methods is different. The condition of the failures in the unimproved groups must also be considered.

The chief reasons for failure of treatment are shown in table 6. A few more patients failed to obtain relief from pain by medical treatment than by surgical procedures. There were also more patients who bled following medical than following surgical treatment, but the difference in this regard is slight. Thus 12.9 per cent bled following treatment with medicine and 8 per cent following surgical intervention. There were eight patients receiving medical treatment who were dissatisfied with the results of treatment, although they were classified as improved. None of the patients who were improved as a result of surgical measures was dissatisfied. This seems to be largely a temperamental factor. Obstruction was as common after surgical as after

TABLE 6.—*Reason for Failure of Treatment*

	Medical		Surgical	
Pain	53		37	
Hemorrhage	24		20	
Obstruction	8		14	
Dissatisfaction	5		..	
Jejunal ulcers	..		6	
Fistulas	..		4	
Death	3	(1.3% of all medical)	19	(6.9%, died following operation)
			7	(died of ulcer later)
			2	(died of secondary operation)

TABLE 7.—*Result of Further Treatment*

	Medical Treatment after Surgical		Surgical Treatment after Medical	
	Number	Per Cent	Number	Per Cent
Good and satisfied	15	31.9	18	35.6
Improved and satisfied	16	34.0	8	15.6
Improved, not satisfied	2	4.2	3	5.8
Unimproved, not satisfied	14	30.0	22	43.1
	47		51	

medical treatment. Failures of a purely surgical nature were as follows: Six had definite jejunal ulcers and four others developed fistulas, three into the colon and one into the duodenum. Three patients who were treated with medicine died from hemorrhage, a mortality of 1.3 per cent. Twenty-eight patients who were treated surgically died: seven of ulcer at some time after discharge; two following operations performed for the repair of gastrojejunocolic fistulas, and nineteen as a direct result of operations for the cure of ulcer. This is a mortality of 6.9 per cent, the total number of operations performed being 275, excluding the cases in which perforation occurred and including the cases that were not followed.

Many patients who have been unimproved by one form of treatment are likely to try another form subsequently. Table 7 shows the results in this group of patients.

Fifty-one patients resorted to surgical procedures after failure of medical treatment, and forty-seven patients who had had surgical treatment took a medical regimen. Seventy per cent of those whose subsequent treatment was medical showed good results or improved, and 57 per cent of those who later chose operation showed good results or improved. Comparison of the results shown in table 7 with those in table 5 shows that medical treatment following surgical treatment gave somewhat better results than medical treatment alone. On the other hand, the results following surgical intervention in cases in which treatment with medicine was unsuccessful were not so satisfactory as in those cases in which medical treatment had not been tried. As a whole, the tables are not so dissimilar. What significance, if any, can be

TABLE 8.—*Results of Various Medical Procedures*

Treatment	Number of Cases	Percentage with Good Results and Satisfied	Percentage Improved and Satisfied	Percentage Improved, Not Satisfied	Percentage Unimproved, Not Satisfied
A. Gastric Ulcers					
Medical treatment undefined	3	....	....	....	100
Six meals and alkali	30	26.7	26.7	3.3	43.3
Sippy treatment advised	2	50.0	....	....	50.0
Sippy treatment partial	3	66.7	....	....	33.3
Sippy treatment complete	3	33.3	33.3	....	33.3
B. Duodenal Ulcers					
Medical treatment undefined	16	25.0	18.7	6.3	50.0
Six meals and alkali	104	23.0	26.9	2.0	48.1
Sippy treatment advised	15	33.3	13.3	....	53.4
Sippy treatment partial	27	37.1	14.8	3.7	44.4
Sippy treatment complete	23	52.0	26.0	....	22.0
C. Coincidental Gastric and Duodenal Ulcers					
Medical treatment undefined	..	.....	.....	....	.....
Six meals and alkali	1	.....	100	....	.....
Sippy treatment advised	1	.....	.....	....	100.0
Sippy treatment partial	1	100.0	.....	....	.....
Sippy treatment complete	2	100.0	.....	....	.....

attached to these figures is not particularly evident. They suggest that a second treatment will again accomplish results similar in proportion to the first, but that the first treatment was not necessarily an unwise choice.

The results of each treatment have been tabulated in tables 8 and 9 according to the location of the ulcer. The various surgical procedures have been grouped under eight heads. Simple excision included complete removal of the ulcer, with or without cautery, and the Heineke-Mikulicz type of pyloroplasty. Gastro-enterostomy alone has been separated from other technical processes often employed with it, such as plication of the pylorus, division (transection) of the pylorus, removal of the pylorus or antrum or both (the Polya or Billroth operations) and excision of the ulcer alone. The Finney type of pyloroplasty was kept distinct. Sleeve resection means the removal of a portion of the stomach with repair in continuity. Various procedures to fit the

particular cases were used in patients with acute perforations, but in order to simplify analysis they have been placed in two groups: with or without gastro-enterostomy. Individuality of procedure was necessarily required in the patients with chronic perforations, and these cases have not been analyzed separately. No operation for subtotal gastrectomy for ulcer was performed in this series.

Medical treatment undefined included the cases of patients who were sent home for treatment by their local physician and in whom the type

TABLE 9.—*Results of Various Surgical Procedures*

Treatment	Number of Cases	Percentage with Good Results and Satisfied	Percentage Improved and Satisfied	Percentage Improved, Not Satisfied	Percentage Unimproved, Not Satisfied
A. Gastric Ulcers					
Simple excision	15	6.7	20.0	13.3	60.0
Gastro-enterostomy	11	18.1	....	18.1	63.6
Gastro-enterostomy and excision	17	58.8	5.9	5.9	29.4
Gastro-enterostomy and resection of antrum	6	16.7	33.3	....	50.0
Sleeve resection	7	43.0	28.6	....	28.6
Pyloroplasty (Finney)	2	50.0	50.0	....	....
B. Duodenal Ulcers					
Simple excision	13	30.7	....	....	69.3
Gastro-enterostomy	78	52.5	7.7	5.1	34.6
Gastro-enterostomy and excision	18	66.7	....	5.5	27.8
Gastro-enterostomy and division of pylorus	14	57.1	7.1	....	35.7
Gastro-enterostomy and excision of pylorus	9	44.4	....	....	55.6
Gastro-enterostomy and plication of pylorus	22	54.5	18.2	....	27.3
Pyloroplasty (Finney)	32	37.5	9.3	12.4	40.6
C. Coincidental Gastric and Duodenal Ulcers					
Excision	2	....	....	....	100
Gastro-enterostomy	1	....	....	....	100
Gastro-enterostomy and excision	1	....	....	....	100
Pyloroplasty (Finney)	1	....	....	....	100
D. Acute Perforation					
Closure and drainage	18	38.8	16.7	33.3	11.1*
Closure and gastro-enterostomy	12	41.7	25.0	25.0	8.3*
E. Slow Perforations					
Various operations	9	33.3	22.2	....	44.4

* Died following operation.

of diet, the number of meals, the medication and the duration of treatment were all unknown.

By "6 meals and alkali," no fixed regimen is indicated. All patients who were given a rather bland diet in five or six feedings daily were included in this classification. In addition, they received varying amounts of alkali, usually consisting of from three to eight doses a day. The length of time they adhered to this schedule varied from three months to two years. Since 1924, the strict schedule of treatment as outlined by the late Dr. Sippy [24] has been used whenever possible.

24. Sippy: Oxford Medicine, New York, Oxford University Press, 1918, vol. 3.

Many of the patients fell short of these requirements, which necessitated different classifications. Those who had "Sippy advised" had the full regimen during only their four weeks' stay in the hospital and discontinued it on discharge. Those who had "Sippy partial" adhered to the treatment fairly well after discharge for a period not exceeding six months. Those who had "Sippy full" took the treatment faithfully for from six to twelve months.

It is impossible to compare the results in tables 8 and 9 too closely owing to the marked inequality in the size of the groups and the differences in the length of follow-up. It is evident, however, that patients with gastric ulcers did not do so well as those with duodenal ulcers. This is not so marked with medical treatment as with surgical. The

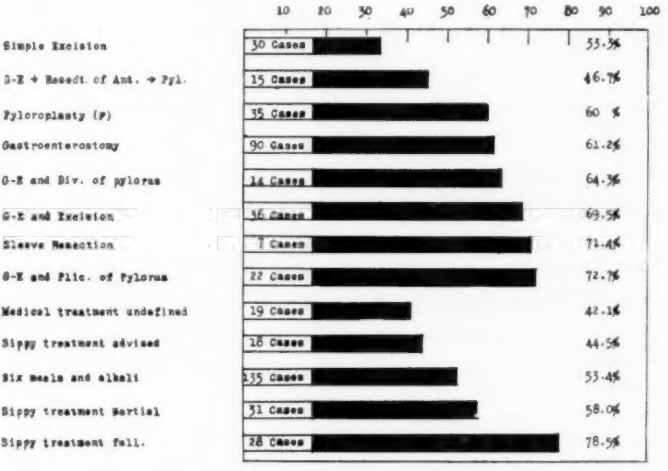

Chart 3.—Results of various treatments in 249 cases of ulcer in which surgical intervention was done and in 231 cases in which medical treatment was used. The shaded areas show the percentages of good and improved cases.

different methods of treatment arrange themselves in the same order of efficiency for the gastric as for the duodenal ulcer.

The results obtained by the various therapeutic procedures are shown in chart 3 in which the shaded areas represent the good and improved cases of both gastric and duodenal ulcers. It shows that of the surgical procedures, simple excision did the least for the patients, and gastroenterostomy with plication of the pylorus did the most. Of the medical treatments, patients in the undefined group did the worst, and the patients receiving a complete Sippy regimen did the best. It must be remembered, however, that the patients receiving the Sippy treatment have been observed for the shortest period.

Surgical methods were in general more effective than medical, but these better results were somewhat offset by the more disastrous consequences in the cases in which surgical measures failed.

COMMENT

The general result of treatment in this group of cases is apparently less satisfactory than that usually reported by others. It may not be so in reality, for similar results can be expressed differently, depending on the means of classification employed or one's point of view concerning the disease. However, one would not expect the result to be poor, since it represents the efforts of an entire hospital staff over a period of more than ten years, and the use of most of the generally accepted forms of therapy. Some forms were more effective than others, but even the best was not so good as most published claims.

For some time it has seemed to us that such claims were unsound. They are not in harmony with the number of dissatisfied patients who return each year. The warm and perennial discussion in medical literature concerning the best method of treatment is sufficient witness that this disheartening experience is by no means local. Any treatment that gives good results in from 85 to 95 per cent of cases, as is frequently asserted, is good, and far better than is available in combating many diseases.

This series of cases consisted, for the most part, of patients whom we have not seen or treated. It was, therefore, the study of a fairly representative group, concerning which predetermined conclusions have not been reached. The results seem more in accord with our ideas of peptic ulcer. The failure of most reports in the literature to agree seems to be either because they are based on an inadequate classification or because the writers fail to appreciate the chronic nature of the disease.

Some generally accepted method of classification is necessary if statistics on treatment are to be compared. This should include, first, a clear definition of the status of the patient, in terms of well recognized criteria. Typical symptoms of ulcer were used in the present study as the most reliable guide, and, as a check, the satisfaction of the patient was determined. The reasons for this have been discussed. Other methods, such as the roentgen examination, have proved singularly unreliable, and they should be used with considerable caution until more is known about them. The length of the period of observation following the completion of treatment also should be stated. This frequently is neglected. Although it was an average of four years in this series, a five-year period would be much better.

The nature of the disease is such that no shorter period can be chosen safely. Whatever the cause or the nature of the remissions may

be, once an ulcer is established it is likely to persist or to recur. The average duration of symptoms of ulcer before treatment in our cases was seven years. This figure is lowered by the small group of patients who were seen shortly after onset because of perforation, hemorrhage or some such striking disability. Many had suffered for a much longer time, several for twenty years and one for forty years. Rarely were the symptoms continuous. Some had had periods of freedom for only a few months, but freedom in others lasted for years, in one for twenty years. In such a case it may be said that one ulcer healed and a new one formed. But when spontaneous remissions vary so greatly in duration, it is difficult to distinguish them from true healing. It is not justifiable to say that absence of symptoms for a few weeks or months constitutes a remission and that absence for more than a year means a cure. A person who has once had an ulcer stands a much greater chance of having the symptoms recur at some later date than if he had never had one, no matter how long he may be free from symptoms. In this sense, at least, the disease is chronic, and it makes little difference under what circumstances a remission is induced. For this reason also, a five year period of observation should be a minimum for reporting cures.

Roentgen examinations often have been sadly misinterpreted in reporting the results of treatment. Disappearance of the gastric niche following treatment has been considered strong evidence for healing, and the infrequent disappearance of the duodenal deformity has been attributed to permanent scar tissue contraction. Critical study of the x-ray observations in cases followed for a long period of time, however, strongly supports the idea that ulcer is a chronic disease. Time and again the gastric niche has been seen to smooth out under the most superficial measures, and to return promptly after the completion of even the most intensive treatments, medical or surgical. One has the impression that any therapy one may use is palliative and not curative.

The appearance of the duodenal ulcer is less easily influenced than that of the gastric ulcer, but the recent conception of the "fleck" ulcer is significant. Several of these cases have been seen at the Peter Bent Brigham Hospital. The patients have had characteristic symptoms of an active ulcer, although the duodenal caps had filled completely and well. Removal of the barium sulphate revealed typical ulcer craters. At subsequent examinations, a deformity might appear and later disappear, only to return again. Yet this defect obviously due to spasm has the same appearance as those deformities attributed to scar tissue. Of the patients in our series who had the usual deformity due to duodenal ulcer, an x-ray picture had been taken in sixty-seven after treatment (both medical and surgical), and only five (or 7 per cent) have shown a return to normal. It is hard to believe that the rest

were cured, since there were persistent roentgen changes; it is easier to feel that those five will later show similar pathologic changes.

Pathologic evidence often has been presented to show that ulcers do heal, but this also may be misleading. Contemporary pathologists do not report scars of healed ulcers as frequently as the older continental workers; so they are more in accord with the clinical evidence of chronicity. The following cases are of interest in this connection.

A laborer, aged 50, came to the Brigham Outdoor Department in May, 1926, complaining of symptoms of ulcer of two year's duration. Roentgen examination revealed a characteristic niche high on the lesser curvature of the stomach. He was advised to enter the hospital for operation, which he did two weeks later. During this interval the symptoms had disappeared, and he was thought to have entered on a remission; nevertheless, an operation was performed. A small area on the lesser curvature was located with difficulty, excised in the usual manner, and the specimen sent to the pathologic department. A Cushing silver clip was then placed on the peritoneal surface of the stomach to mark the location of the ulcer. The pathologic report was that of a healing, almost healed ulcer. Despite this fact, an x-ray picture taken five days after operation revealed a defect similar to that before surgical intervention, and located in the same spot as shown by the clip. Symptoms recurred in two months, and both the symptoms and the x-ray observations have remained the same to date. In the second case, typical symptoms returned nine and a half years after excision of a gastric ulcer, and roentgen study showed the lesion in exactly the same place as before, as far as could be determined.

More observations of this kind are needed, but these are enough to throw doubt on the value of a pathologic report, as far as the cure of the disease is concerned. They suggest that the local ulcerative spot may undergo healing processes rapidly. They suggest further that remissions in the symptoms actually may be accompanied by a quiescence of the ulcerative process. We have been prone to regard the disease of ulcer as a local disorder in the gastro-intestinal tract. In reality, the evidence points to the ulceration as a local manifestation of a deep-seated disorder. This would explain the rapid return of an ulcerative condition following surgical removal of an ulcer and particularly, a return to the same site.

These considerations will be clarified only when a deeper knowledge of the disease is gained. Then, too, we shall possess a better treatment; for all of our present methods primarily relieve symptoms, except when perforation or some mechanical defect has occurred. This is evident when one compares the general result of all treatment with the results in the group to which treatment was not given (table 5). The former showed only 10 per cent more improved cases. Careful study of the other figures in the table shows that the two groups are not dissimilar.

The results of surgical treatment have been better than those of medical treatment and a study of the various operative methods used shows that the most successful were those which changed the local

condition most. This may be due to a correction of the factors that are responsible for the symptoms rather than to any curative effect on the disease itself. For example, many of our patients on whom gastroenterostomies have been performed have been entirely free from distress except during periods of unusual emotional strain (automobile accidents, death in the family, financial worries) or acute infections (colds, etc.). Others have had massive hemorrhages months and years after operation without any warning symptoms. We have been unable to escape the feeling that the disease in each instance has persisted, although the patients are, on the whole, comfortable.

We do not mean to imply that treatment has not been worth while, for much can be done for the patient with ulcer. His life may be saved in case of perforation. Obstruction can be overcome. His symptoms can be relieved, and he is enabled to lead a normal existence. It is beyond the scope of this paper to discuss the indications for the various methods of treatment. Each has its advantages and its disadvantages, and both must be carefully weighed with reference to the particular case at hand. But it is important to remember that cure cannot be promised with any of these methods. To advocate any one method in preference to all the others and to claim a high percentage of permanent relief is not justified by the results.

A patient with ulcer is notoriously of a wandering disposition. He goes from one physician to another in search of a cure. A return of symptoms leads him to consult some one else, who may understand his case better. The new advice is often different from the old, and is again accompanied by the assumption that rigid adherence to the new regimen will be followed by permanent results. This causes an unsatisfactory state of affairs. The physician is led to believe that his treatment has been efficacious, since the patient does not return. The patient loses confidence.

This situation could be much improved by a realization that patients with peptic ulcer have a truly chronic disease, not unlike diabetes mellitus or chronic nephritis, for which no cure is known. The present methods of treatment will then be used with more discretion, and the patients, being informed of their prospects, will be transformed into a cooperative group. In this way, better results will be obtained than in the past. Cure can come only when the real nature of the disease is understood, and when a method is devised which strikes at the cause and not at the symptoms.

SUMMARY

An analysis of 556 cases of chronic peptic ulcer seen during the years 1913 to 1926 is presented. Figures concerning the incidence, symptomatology, laboratory observations and complications are given.

Hyperacidity occurred in 50 per cent. There was only one proved case of achlorhydria, and in this the diagnosis of ulcer was made only by the x-rays, there being no symptoms of the disease.

The x-rays failed to show evidence of an ulcer in thirty-six cases (7 per cent).

Hemorrhage occurred in 194 (34.8 per cent) of the cases and was the cause of death in eight. Seventy-seven of this group had more than one hemorrhage. It was the first sign of the disease in twenty-five. After a rather high incidence in the first two years of symptoms, the proportion fell to 23 per cent and remained there.

Acute perforation occurred in thirty-eight patients, eleven of whom (28 per cent) died. There was no tendency for this complication to appear early in the course of the disease.

Cancer was found in six of the 135 cases of gastric ulcer (4.4 per cent); of these, three apparently developed from the ulcer.

Retention occurred in 135 cases, ninety-two being due to pyloric spasm.

Hour-glass deformity occurred in sixteen.

No greater incidence of foci of infection was found in this group than in the general hospital population.

Ulcer was the cause of death in forty-one cases to date: twenty-one patients died following operation.

The results of all forms of treatment showed that about 60 per cent of the patients were relieved after an average observation period of four years. The strict Sippy treatment proved to be the best of the medical methods, and gastro-enterostomy with plication of the pylorus the best of the surgical methods. Surgical measures were somewhat more effective than medical, but this was offset by the fact that the results in the cases in which surgical measures were employed were worse than the ones in which medical treatment was given.

All evidence points to the fact that ulcer is a chronic disease and that all the present methods of treatment are merely palliative. Cure probably is rare. Each method has its advantages and disadvantages, which must be weighed in the individual case. The best results are to be expected from a wise choice of these methods, the education of the patient concerning the nature of his condition and the amount of relief that can be expected.

SOME MEDICOLEGAL ASPECTS OF OCCUPATIONAL DISEASE *

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In the past five years, New Jersey has experienced the occurrence of fatal cases of occupational poisonings in new industrial diseases or in new forms of old diseases, which has called attention to the present inadequate method of compensating workmen through a schedule of specific diseases. This list of occupational diseases in New Jersey includes: anthrax; poisoning from phosphorus, benzol and its homologous, wood alcohol, lead, mercury, arsenic and chromium; caisson disease and, recently, radium necrosis.

The types of poisoning I shall discuss are tetra-ethyl lead and benzol poisoning and radium necrosis.

In 1923, two factories in New Jersey manufactured tetra-ethyl lead, a volatile liquid substance which is added to gasoline to give greater compression and hence more power to motors. The strength of this substance may be estimated from the fact that one gallon of tetra-ethyl lead is added to 5,000 gallons of gasoline to make the proper solution for high compression motors. The crude manner in which it was at first manufactured exposed workmen to its deadly effect. Of twenty-eight men directly exposed to this substance, six died from a severe form of lead encephalopathy, many of them having convulsions, four are now in asylums for the insane and sixteen have various permanent disabilities such as cranial and peripheral nerve palsies, nephritis and marked loss of weight and strength. One man has been under my care for three years. Before the onset of the lead poisoning he weighed 185 pounds (83.9 Kg.); he now weighs 125 pounds (56.7 Kg.), and has a double paralysis of the seventh and motor roots of the fifth cranial nerve. Mentally, he alternates between states of excitement and depression and is often forced to perform impulsive acts almost involuntarily. Although injury due to lead poisoning was compensable under the law of New Jersey at the time, sixteen of the persons who were affected by the poison elected to sue under the common law on the basis that tetra-ethyl lead was a new poison not listed under the compensation law. The cases were never decided by law since they were all settled out of court for large sums. At the present time, only one fac-

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tory in the country makes tetra-ethyl lead by a process which from start to finish is completely closed so that the worker is not exposed. Since the establishment of this plant, no new cases of tetra-ethyl lead poisoning have been reported.

The occurrence of thirteen fatal cases of benzol poisoning in the past year and a half has called attention to a widespread occupational hazard that may soon rival that of lead poisoning. Two of the deaths occurred in the sulphonation of benzine during the synthetic production of phenol: one of these was a watchman in the factory, and the other a helper working near one of the mixing vats. Three men, including the original cleaner and the two men who went to his rescue, died after cleaning out a single tank that had contained drip oil with benzol. All three neglected to wear masks or to carry emergency ropes. It was interesting to note the different effect of the benzol in these two instances. In the first instance, both men were found narcotized and died several hours later without gaining consciousness. In the second instance, the three men were found dead and were apparently asphyxiated almost at once, probably owing to the exclusion of air on account of the large concentration of benzol fumes. The remaining cases were those of chronic benzol poisoning occurring in three separate factories, all of which were making artificial leather by the application of a dope or mixture containing nitro-cellulose bases dissolved in a vehicle of benzol to a fabric or cloth. The latter cases occurred in men who had worked for varying periods of time, from a few weeks to several years, and who were exposed to varying concentrations of benzol fumes. They all succumbed to an aplastic leukopenic anemia, with buccal sepsis, and multiple hemorrhages from the skin and the mucous and serous membranes. Following the occurrence of these fatal cases, 110 different claims were made for compensation for alleged benzol poisoning. Since the condition can hardly be diagnosed in its early stages, the difficulty of arbitrating these cases became great.

The following postulates were taken for a standard and guide in New Jersey: 1. The claimant must demonstrate an exposure to benzol poisoning. 2. The claimant must present symptoms of benzol poisoning. 3. The claimant must demonstrate a change in his blood picture.

A tentative diagnosis of benzol poisoning was made when the claimant satisfied the first two postulates, while a positive diagnosis was made in the presence of the characteristic blood changes.

Clinically, the symptoms may be divided into three groups: (1) those due to local irritation such as conjunctivitis, bronchitis and stomatitis; (2) those due to the effects of blood disturbances or anemia such as pallor, muscular weakness, gastric disturbances, dizziness, petechial hemorrhages, purpuric spots, menstrual disturbances and occasionally cyanosis; (3) those due to nervous symptoms such as muscular tremor,

inebriation, insomia, hallucinations and euphoria. None of these symptoms are pathognomic, although a grouping of many may lead to a diagnosis. Most reliance is placed on the blood picture which may show only a secondary leukopenic anemia in the early stages. Of 289 men examined in an artificial leather factory, 46 showed a definite secondary leukopenic anemia; some of the blood counts were as low as 2,800,000, the white cell counts as low as 3,300 and the hemoglobin contents as low as 30 per cent. When the continued effect of benzol finally paralyzes the hematopoetic centers in the bone marrow, an anemia of the aplastic or a regenerative type develops, characterized by an extremely low red and white cell count, as low as 500,000 red cells, 500 white cells and 15 per cent hemoglobin, an absence of new forms and a marked reduction of the blood platelets. As a result hemorrhages occur from the mucous membranes, usually with a fatal outcome.

The widespread use of benzol in the artificial leather industry, the rubber industry, and in the manufacture of sanitary cans, and the harmful effects of its use have caused industry in New Jersey to cooperate with the department of labor in correcting this trouble by abandoning the use of benzol and substituting for it less toxic solvents such as xylol, toluol and high flash naphtha at an only slightly increased expense. This year there were only nineteen new cases reported and two deaths listed among the thirteen referred to in the foregoing paragraphs.

In 1923, the first cases of radium poisoning were referred to the rehabilitation clinic. One woman, aged 24, had worked for seven years as a dial painter, during which time she pointed the brush she used with her lips, thereby ingesting some of the radioactive substance that had been added to the zinc sulphide paint to make it permanently luminous.

Chronic anemia with extensive necrosis of the inferior maxilla developed. Her blood picture showed profound anemia with a color index of one plus, a large cell anisocytosis with many macrocytes, a slight polychromatophilia, occasional granular basophilia and a scant number of nucleated red cells and a rare megaloblast. The blood platelets were normal, and purpura or bleeding was not elicited. The icterus index and van den Bergh tests were negative, showing that the anemia was not due to hemolysis but to a lack of production of the ordinary blood forms. After an illness of three years, she died from a progressive anemia with extensive necrosis of the lower and upper maxillae and a terminal bronchopneumonia. Autopsy, by Martland, showed intense replacement of the normal adult fatty marrow by a red, regenerating bone marrow. The organs were tested after incineration for radioactivity and showed storage of radioactivity in the bones to a large extent and to a lesser extent in the spleen and liver.

Since this case, eleven other patients who were exposed died; five others are still alive, but they are suffering from severe anemia. The absence of a provision in the Workmens' Compensation law made the latter resort to common law for redress, so settlements have been made by the company. The disease is now included in the compensation law.

In view of the limited knowledge and comparatively few cases of radium necrosis adequately studied, I have been unable to set up any diagnostic standards. However, for the purpose of guidance the following factors must be considered:

1. History of exposure to radioactive substances.
2. Symptoms of anemia including the blood picture.
3. Local symptoms of a jaw necrosis or radiation osteitis.
4. Physical tests of radioactivity:
   (*a*) Autoradiography.
   (*b*) Electrometer test both to expired air in the living and to incinerated bone after death.

These are some of the problems that the individual medical examiner or expert must meet in arbitrating claims for compensation. To recapitulate, new diseases or new disease schedules are made without acquaintance with the physiologic action of the poisons mentioned. There is a marked lack of interest and cooperation on the part of the members of the medical profession on whose reports one must often depend for important information. Many are unfamiliar with the field of industrial medicine and send clinical or laboratory reports which are inaccurate or which, having been performed too late, are useless. Through incorrect diagnoses many workmen who are suffering from occupational diseases called by other names are being deprived of their just compensation. Furthermore, there are no existing standards on which one can rely for guidance such, for example, as the definition of lead absorption and lead intoxication. The work of such committees as the South Africa Committee on Silicosis and the Standards Committee of the American Public Health Association is a step in the right direction.

OPIUM ADDICTION

V. MISCELLANEOUS OBSERVATIONS ON HUMAN ADDICTS DURING THE ADMINISTRATION OF MORPHINE *

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In this paper we wish to present further results obtained from a study of a series of male opium addicts made while we were supplying their needs with morphine. These studies include fractional gastric analysis, roentgen examination of the gastro-intestinal tract, functional tests of the liver, dextrose tolerance tests, chemical and microscopic examinations of the urine, phenolsulphonphthalein tests and studies of the basal metabolic rate, temperature, blood sugar response to morphine and to epinephrine and the results of roentgen examination for persistent thymus.

FRACTIONAL GASTRIC ANALYSIS

The secretory response of free and total acid of the stomach to the standard Ewald test meal was studied by the fractional method in eighteen different addicts. In all cases, samples of gastric juice during fasting were removed for analysis. Table 1 gives the results obtained in these cases for the contents both during fasting and at intervals of fifteen minutes following completion of the meal. As seen from the tables, both the free and the combined acid of the gastric juice during fasting varied considerably. An analysis of the individual cases showed that in six no free hydrochloric acid was present during the fasting stage. Four of these six cases still failed to show the presence of free hydrochloric acid fifteen minutes after the test meal was given. In one case, no free acid was found during the entire period of 105 minutes following the meal, while in two others in this group only small quantities were found. The other twelve cases presented a normal response of

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* From the Narcotic Wards of the Philadelphia General Hospital.

* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, the work was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital, which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

the free hydrochloric acid when compared to the observations of Rehfuss.[1]

All cases showed the presence of a certain amount of total acid in the gastric juice during fasting. The curves in chart 1 show the average of the total acid and free hydrochloric acid compared to the normal isotrophic curve of Rehfuss.[1]

A comparison of these curves shows that the curves representing the total acid of the addicts are much higher while the patient is fasting than are the normal curves, while the free hydrochloric acid is always at practically the normal level. The response of the secretion of both the

TABLE 1.—*The Fractional Gastric Analysis in Eighteen Cases of Opium Addiction During the Administration of Morphine*

Case No.	Fasting		15 Min.		30 Min.		45 min.		60 Min.		75 Min.		90 Min.		105 Min.	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
26- 1	21	34	6	24	8	32	32	50	..	..	21	40	61	86	..	..
26- 2	0	16	0	15	0	13	11	28	12	30	18	44	23	50	24	50
26- 3	12	33	14	40	20	51	12	37	43	71	23	47	21	43	..	.
26- 5	19	41	34	52	58	76	42	70	52	71	21	42	7	17	7	19
26- 6	6	11	7	22	21	44	28	60	56	85	37	63	40	61	40	60
26- 7	11	23	8	28	16	50	13	50	27	71	29	78	32	78	32	76
26- 9	0	14	0	17	5	23	0	20	0	28	11	35	29	58	27	54
26-10	31	45	10	27	7	25	4	26	2	28	0	30	0	22	0	23
26-11	13	33	0	22	4	27	12	31	41	75	40	76	45	79	46	77
26-12	0	14	0	11	0	12	0	26	0	15	0	12	0	12	0	13
26-13	0	11	4	27	22	44	30	58	48	77	31	58	28	56	39	69
26-15	0	17	0	16	4	16	18	41	25	44	23	41	13	32	0	16
23-16	0	31	0	11	0	11	0	14	4	17	5	20	3	18	0	17
26-17	28	50	55	70	45	66	43	68	37	63	40	64	41	67	42	72
26-19	25	51	16	39	12	47	19	41	20	48	21	49	25	51	24	54
26-31	10	29	8	25	20	42	50	71	57	83	59	80	46	66	24	39
26-22	47	75	47	70	52	77	53	81	48	84	57	90	60	93	60	94
26-24	24	75	18	78	41	67	50	74	38	56	13	42	11	26	16	30
Average	13.7	34.0	12.6	33.0	18.6	40.1	23.1	47.5	30.0	55.6	21.6	50.5	23.9	50.8	23.8	47.8

free and the total acids is much slower in the addict and does not reach the magnitude of the normal curve. Both, however, reach their peaks at the same time as do the normal curves and decline at the same rate. There was no correlation between the variations in the different individual responses and the amount of drug administered or the history of length of addiction.

ROENTGENOGRAMS OF THE GASTRO-INTESTINAL TRACT

Through the courtesy of Dr. E. Burville-Holmes, in charge of the x-ray work in the Philadelphia General Hospital, we had sixteen patients

1. Rehfuss, Martin E.; Bergheim, O., and Hawk, P. B.: The Fractional Study of Gastric Digestion with a Description of Normal and Pathologic Curves, J. A. M. A. **63**:909 (Sept. 12) 1914.

examined after the usual barium meal in order to gather what information we could as to the movements of the stomach and the speed of passage of the barium along the gastro-intestinal tract. The results obtained showed that in the sixteen patients there was but one with definite ptosis of the stomach; this patient also showed marked atony. He also failed to show the presence of any free hydrochloric acid when subjected to the fractional test meal. Five cases exhibited hyperperistalsis and three hypoperistalsis, the peristaltic movements in the other cases being normal. Five cases showed slight atony of the muscular wall. Not any of the cases showed the presence of any organic lesion,

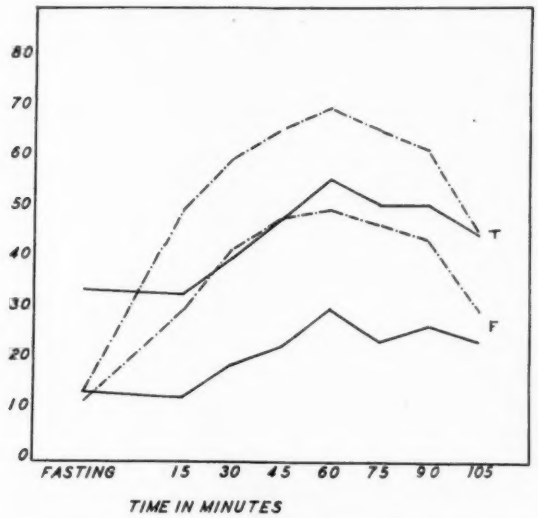

Chart 1.—Average response to a standard test meal of the gastric secretion of a group of human addicts receiving morphine, compared to the normal isotrophic curve of Rehfuss. *T* indicates total acid and *F*, free hydrochloric acid. In this chart and in charts 2 and 3, the solid line indicates addicts and the broken line, normal persons.

the conus being normal and pylorospasm absent. In three cases, the barium failed to reach the ileocecal valve during the six hours following the ingestion of the barium. In one of the remaining thirteen cases, the barium had reached the hepatic flexure and in two the splenic flexure; in the rest, it was found in the cecum at the end of six hours. In these studies there was again no correlation in the behavior of the gastrointestinal tract and the length of addiction or the amount of drug used by the different patients in a twenty-four hour period.

LIVER

The phenoltetrachlorphthalein test of the function of the liver as devised by Rosenthal [2] was carried out in ten different addicts. In eight of the ten, the dye disappeared from the blood stream in less than one hour, the normal time of disappearance. At the end of one hour, there was still 3 per cent left in one case, and 0.9 per cent in the other. At the end of two hours, one case still showed the presence of 1 per cent of the dye. Van den Bergh's test [3] was negative in nine cases studied. The icterus index of the serum showed an average of 5.2 and varied from 3 to 9 in ten cases studied. The average normal of this test as devised by Murphy [4] is given as from 4 to 6.

DEXTROSE TOLERANCE TEST

Ten different addicts were selected to determine the rapidity of rise and fall of dextrose in the blood following its ingestion by mouth.

TABLE 2.—*Results of Phenoltetrachlorphthalein, van den Bergh, Icterus Index and Dextrose Tolerance Tests in Human Addicts During the Administration of Morphine*

	Phenoltetrachlorphthalein			Van den Bergh	Icterus Index	Dextrose Tolerance, Mg. per 100 Cc. of Blood			
	15 Min.	1 Hour	2 Hours			Fasting	15 Min.	1 Hour	2 Hours
Number of cases.....	10	10	10	9	10	10	10	10	10
Highest.....	8%	3%	1%	..	9	120	128	170	157
Lowest.....	4%	0%	0%	..	3	96	102	98	101
Average.....	5.8%	0.9%	0%	Negative	5.2	107	121	130	127

Each addict was given 1.75 Gm. of dextrose per kilogram of body weight. The average results obtained are found in table 2 and are plotted in chart 2, which also contains a normal curve. The peak of the curve is reached at the end of an hour, and the curve is still elevated at the end of two hours as compared to the normal curve shown for and derived from normal patients in the Philadelphia General Hospital. A study of the individual cases shows a striking uniformity of the curve in all but two of the cases. In one of these, the blood sugar rose to 170 mg. per hundred cubic centimeters of blood at the end of one hour, while the other reached its peak of 157 mg. only at the end of two hours. One

2. Rosenthal, S. M.: New Method of Testing Liver Function with Phenoltetrachlorphthalein, J. Pharm. & Exper. Therap. **23**:385 (June 5) 1924.

3. Van den Bergh, quoted by McNee, J. W.: Jaundice: Review of Recent Work, Quart. J. Med. **16**:390 (July) 1923.

4. Murphy, William P.: Biliary System Functional Tests, Arch. Int. Med. **37**:797 (June) 1926.

case studied showed a decided decline in blood sugar of from 128 to 98 mg. in the period of fifteen minutes and one hour after the dextrose was given. The dosage administered to these addicts ranged from 5 to 16 grains (0.32 to 1.04 Gm.) of morphine sulphate in a period of twenty-four hours with no correlation between the amount of the drug and differences in the results.

KIDNEY

The urines of 100 addicts were subjected to the usual chemical and microscopic examination. All specimens examined were taken from the first urine passed in the morning before breakfast. The specific gravity varied from 1.014 to 1.035, the average for the 100 cases being 1.022 with nothing significant in the color. Sugar, as determined by Benedict's method, was not found in a single case. Seventeen of the 100 cases

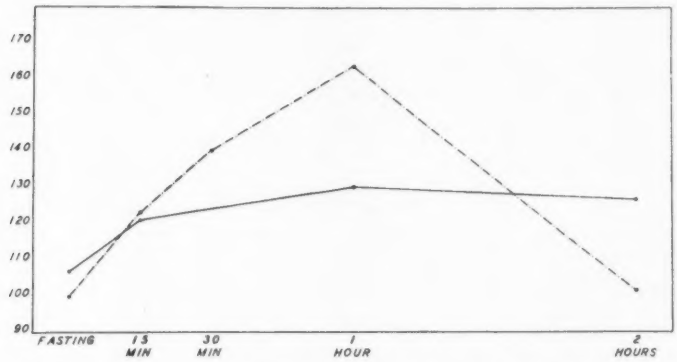

Chart 2.—Average blood sugar response to the ingestion of 1.75 Gm. of dextrose per kilogram in a group of human addicts receiving morphine, compared to a series of normal persons.

showed from a faint trace to a trace of albumin. Of these seventeen cases, only four showed the presence of a few hyaline casts. In eighteen cases there was an excess of leukocytes, while in one case a few red blood cells were found.

The phenolsulphonphthalein test of kidney function, in which the dye was injected into the lumbar muscles, was carried out in twenty different addicts. The average elimination of the dye was 56 per cent in two hours, the average for the first hour being 42 per cent and for the second hour, 14 per cent. The lowest elimination found was 22 per cent in the first hour and 10 per cent in the second hour. The urine of this addict was free from albumin and sugar, and the blood urea nitrogen was 12 mg. per hundred cubic centimeters of blood. The most rapid elimina-

tion found was 52 per cent in the first hour and 22 per cent in the second, or a total of 74 per cent in two hours. Five of the cases showed an elimination of less than 50 per cent in two hours. All cases studied showed the greatest percentage of excretion in the first hour.

Six cases were selected and studied in which the total intake of food and water was limited to the same amount and character and given at the same period of the day. The same procedure was also carried out in three normal nonaddicts. The total quantity of urine excreted in twenty-four hours compared favorably with the total quantity excreted by the normal patients.

BASAL METABOLISM

Sixty-eight determinations of the basal metabolic rate were made on twenty-five different addicts. A number of additional determinations

TABLE 3.—*Basal Metabolic Rate of Twenty-Five Addicts Grouped According to the Amount of Morphine Used Per Twenty-Four Hours*

	Amount of Drug Used in 24 Hours									
	0 to 4 Grains		5 to 9 Grains		10 to 14 Grains		15 to 19 Grains		20 to 24 Grains	
Basal metabolic results	18 to 33	−14 to 4	−14 to 10	− 3 to −22	− 7 to 12	9 to 15	− 5 to −16	3 to 6	−10 to −13	−14 to −25
			−11 to 16	−13 to 2	−12 to −28	− 1 to 11	−15 to 9	5 to 8		
			8		9 to −26	− 6 to 8	14			
					13 to 6	24				
						20				
						4				
						5				

had to be discarded on account of obvious poor cooperation on the part of the patient. Prof. August Krogh's basal metabolism recording apparatus was used for this work. The accuracy of this apparatus was checked several times a week with a person whose metabolism was known to be normal. The number of determinations accepted for each person varied from a single determination to as high as four in several cases. The majority, however, were always studied until at least two determinations were obtained on separate days. The oxygen consumption was studied over a period of ten minute intervals.

Table 3 has been arranged in order to show the variations of the metabolism according to the amount of drug used in a twenty-four hour period. It will be noted that with the exception of the persons using more than 20 grains (1.3 Gm.) in a twenty-four hour period and the two using less than 4 grains (0.26 Gm.) in the same period, the extremes obtained above and below normal are practically the same, namely, — 28 per cent and + 24 per cent. Both persons using more than 20 grains of

morphine a day showed decreases in the basal metabolism ranging from — 10 per cent to — 13 per cent and — 14 per cent to — 25 per cent, respectively. One of the patients using only 4 grains daily had the greatest increase, namely, + 33 per cent. The cooperation at both extremes seemed to be excellent; yet we are inclined to the belief that when large quantities of the drug were used, there was considerably less nervousness than in the case in which only 4 grains were used in the twenty-four hour period.

The average variation of the entire group of sixty-eight determinations ranged from — 12 per cent to + 11 per cent, which compares favorably with the normal variation of from — 10 per cent to + 10 per cent. Thirteen of the thirty-nine results obtained in which the metabolism was found to be decreased were lower than the average low of — 12 per cent, and fourteen of the twenty-nine results obtained in which the figures ranged in the positive direction were above 12 per cent.

TEMPERATURE

The average temperature taken with the thermometer in the closed mouth underneath the tongue in 100 cases was found to be 98.3 F. The highest temperature reported was 98.9 and the lowest, 97.8. The rectal temperature taken in ten cases varied from 98 to 99.6, with an average of 99.2. All patients selected were free from abscesses and intercurrent infection.

THE EFFECT OF A SINGLE DOSE OF MORPHINE ON THE BLOOD SUGAR OF THE ADDICT

Six addicts were selected from whom blood was drawn in the morning prior to the time at which the first regular injection of morphine was

TABLE 4.—*Average Response of the Blood Sugar in Human Addicts to a Single Dose of Morphine*

Number of Cases	Basal	After Injection				
		15 Minutes	30 Minutes	1 Hour	1½ Hours	2 Hours
6	84 mg.*	89 mg.	93 mg.	92 mg.	95 mg.	93 mg.

* Milligrams per hundred cubic centimeters of blood.

due. They were then given their regular dosages, and samples of blood were taken at intervals of fifteen minutes, thirty minutes, one hour, one and a half hours and two hours following the injection. The samples of blood were analyzed for sugar content. Table 4 gives the average results obtained, showing the effects to be negligible, the slight rise present being within the limit of error of the method used [5] for analysis. Two additional

5. Folin, Otto; and Wu, Hsien: A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367 (March) 1920.

cases were selected and the same procedure followed except that the dosage given was double the amount that would have been given ordinarily. The results obtained in these two cases were identical with those obtained in the six cases in which the normal dosage was given, namely, an insignificant rise in the quantity of sugar present in the circulating blood.

THE EFFECT OF EPINEPHRINE ON THE BLOOD SUGAR OF ADDICTS COMPARED TO ITS EFFECT ON THAT OF NORMAL PERSONS

Five addicts were selected in order to determine the degree of response in the rise of the blood sugar to a standard injection of

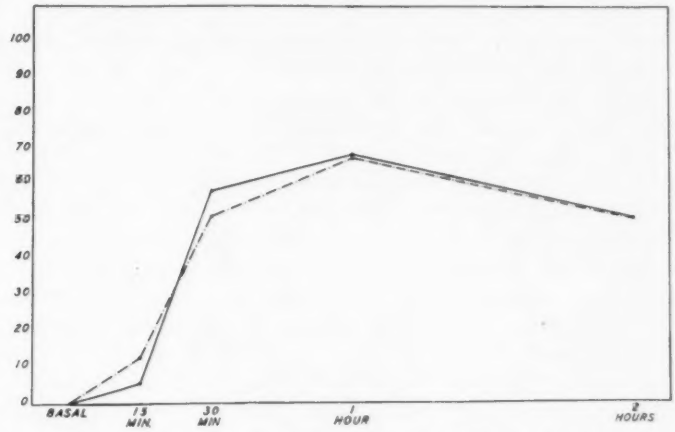

Chart 3.—Average blood sugar response to the injection of 1 cc. of epinephrine hydrochloride (1 : 1,000) in a series of human opium addicts receiving morphine, and in a group of normal persons.

epinephrine, namely, 0.001 Gm. of epinephrine hydrochloride. In order to obtain a comparison, the same solution was used in five normal persons.

Chart 3 shows a comparison of the relative rise of the blood sugar taken at fifteen minute, thirty minute, one hour, and two hour intervals. It will be noticed that the curves are practically identical, showing no difference in the response of the rise in sugar in addicts as compared to that of normal persons. The epinephrine was always given at an interval of fifteen minutes following the injection of the regular dosage of morphine sulphate. We have shown in the preceding paragraph that morphine per se does not cause a rise in blood sugar. The effect of the

epinephrine on the blood pressure of both addicts and normal persons was measured, but wide fluctuations in both groups did not justify the drawing of any conclusions.

THYMUS

Roentgen studies to detect the presence of persistent thymus were made on ten addicts. The results in all cases studied were negative. From the clinical evidence there was no reason to suspect the presence of the thymus in any of our cases.

COMMENT AND LITERATURE

The results obtained in our studies of the stomach by means of the x-ray and fractional analysis of the gastric juice indicate little change in the behavior of this organ as the result of prolonged usage of opium or its derivatives. Sollier [6] asserted that not only does morphine stimulate the function of the gastric glands, but it also increases the tonicity of the stomach, and that as soon as the drug is withdrawn the stomach dilates. Morat [7] called attention to the markedly affected condition of the digestive tract, pointing out that the salivary secretion was much lessened, and that the gastric and intestinal glands suffered no less. Bishop [8] described the impaired digestion of addicts. The degree of atony present in four of our five cases was so slight as to demand little attention, so that only one of our sixteen cases showed any marked change in the muscular tone of the stomach. The same comment may be made concerning the peristaltic movements; in five cases a degree of hyperperistalsis and in three cases hypoperistalsis were present.

We do not believe that the secretion of the gastric juice is impaired to any great extent. There was a delay in four of the eighteen cases studied, and the average total response was less than the isotrophic response of Rehfuss.[1] Thirteen of our cases showed a normal response, the quantity secreted being well within the normal limits.

The rate of progression of the barium through the small intestine was decreased in three cases. This delay in movement is undoubtedly significant and may perhaps be attributed to the action of the drug, but it is not universally present, as in the other sixteen cases the movement of the barium was normal.

In 100 per cent of our cases in the ward daily evacuation of the bowels did not occur without the aid of a cathartic. This marked con-

6. Sollier, P.: La demorphinisation et le traitement rationel de la morphinomanie, Semaine méd., 1894, pp. 146-152.

7. Morat, D.: Le sang et les sécrétions au cours de la morphinomanie et de la désintoxication, Paris, G. Steinheil, 1911, p. 180.

8. Bishop, E. S.: Narcotic Drug Problem; Pathology, Pathognosis and Treatment, Philadelphia, F. A. Davis and Company, 1913, p. 524.

stipation is one of the few universally accepted characteristics of the behavior of the gastro-intestinal tract of addicts. We have had statements from addicts that their bowels move each day without the aid of cathartics or enemas, but in practically every case the movement was brought about because the addict refrained from the drug until a movement occurred. While the drug is being administered in the ward, we have always been forced to give relief in the form of medication or enemas.

The only manifestation that may be regarded as abnormal which we have been able to detect in the behavior of the kidney is that in seventeen of the 100 cases studied an amount of albumin ranging from a faint trace to a trace was found. Only four of these cases showed a few hyaline casts. This is in partial agreement with Levinstein [9] and Sollier,[6] who asserted that albuminuria was frequently present in opium addicts. Morat,[7] however, came to the conclusion that it was a common error to regard albuminuria as being present in morphinism. The impairment of the phenolsulphonphthalein excretion in only one case and possibly slight impairment in four cases does not point to serious impairment of the kidneys as ascertained by means of this test. Studies of water balance [10] convinced us that the amount of urine secreted by the kidneys of addicts compares favorably with that of normal persons, and we do not agree with Lambert [11] that the quantity of urine secreted becomes diminished after prolonged addiction. Addicts will perspire freely when using more or less than the necessary amount of the drug to prevent withdrawal symptoms, but when the drug is administered as we employed it in our water balance experiments, the ratio of fluid secreted by the kidney to the insensible loss is the same as in a normal person. The absence of the dextrose is in agreement with the normal blood sugar content and also rules out renal glycosuria.

Impairment of liver function in the addict is also practically negligible as measured by the phenoltetrachlorphthalein test of Rosenthal [2] as well as by the negative results of the icterus index and van den Bergh tests. Bell [12] claimed the presence of fatty degeneration of the liver, and Morat [7] and Sollier [6] often found tenderness over the liver and in many cases increase in its size. In addition to the results obtained

9. Levinstein, E.: Die Morphiumsucht, translated by Charles Harrer, 1878.

10. Light, Arthur B., and Torrance, Edward G.: Opium Addiction: IX. Water Balance Studies During the Administration and Withdrawal of Morphine, Arch. Int. Med., to be published.

11. Lambert, A.: Chapter in Osler and McCrae: Modern Medicine, Philadelphia, W. B. Saunders Company, 1914.

12. Bell, F. McKee: Morphinism and Morphinomania, New York M. J. **93**: 680, 1911.

by tests, we have shown that the liver in the addict still responds with a degree of glycogenolysis following the injection of epinephrine hydrochloride quite comparable to that in normal persons. The rate of both rise and fall of the blood sugar in the dextrose tolerance test is somewhat delayed and is of sufficient interest to commend further study. The injection of morphine per se does not bring about any rise in the blood sugar in addicts and is in agreement with the observations of Plant and Pierce,[13] who found that when addiction became established in dogs the ability of a single dose of morphine to bring about a response in blood sugar disappeared.

Conclusions as to the basal metabolism in opium addicts during the administration of a sufficient amount of the drug to supply their needs is rather difficult in view of our observations. The average of the sixty-three determinations on twenty-five different addicts falls within the normal range. Yet there are many individual determinations that will range above or below the high and low normal figures. Unfortunately, we have only two cases in which the amount of drugs taken during twenty-four hours was below 4 grains and only two in which the amount is more than 20 grains, while most of our determinations were made on addicts who needed between 5 and 20 grains a day. The cases in which both limits of dosage per day were given would suggest that using small dosages did not decrease the metabolism and, if anything, increased it, while the cases in which the large dosage was given exhibited a decrease in the metabolism. Undoubtedly we were dealing again with one of the most difficult phases of the problem of drug addiction, namely, the quantity required to prevent withdrawal symptoms and arrest the "nervousness" of which these unfortunate people complain and which we are not able to measure. We are quite certain from our experience that an additional amount of the drug beyond a certain required dosage brings about a state of both mental and physical relaxation which undoubtedly will bring metabolism to its basal level and perhaps lower. If, on the other hand, the quantity is insufficient even though the patient may relax and remain quiet during the actual determination, the emotional disturbances which these people undoubtedly have may increase the metabolic rate above the normal level. There was no correlation between the basal pulse rates and the level of the metabolic rate.

CONCLUSIONS

Studies of the stomach, kidney, liver, basal metabolism, thymus, temperature, dextrose response to epinephrine and dextrose response to

13. Plant, O. H., and Pierce, I. H.: Studies in Chronic Morphine Poisoning in Dogs. III. The Blood Sugar During Tolerance and Withdrawal, J. Pharm. & Exper. Therap. **33**:371 (July) 1928.

morphine revealed no fundamental differences from normal in addicts to whom morphine was administered to supply their needs, except a slight delay in the average response of gastric secretion to a test meal, the presence of albumin in the urine in 17 per cent of the cases and wide fluctuations of the individual determinations of basal metabolism, although the average metabolic rate was within normal limits. A delay in the return of the blood sugar to normal following the ingestion of dextrose given by mouth was also noted.

Book Reviews

THE FUEL OF LIFE: EXPERIMENTAL STUDIES IN NORMAL AND DIABETIC ANIMALS. By JOHN JAMES RICKARD MACLEOD, M.D., LL.D., D.Sc., F.R.S., Professor of Physiology, University of Toronto, Canada. Louis Clark Vanuxem Foundation. Lectures delivered at Princeton University in March, 1928. Price, $2.50. Pp. 147. Princeton, N. J.: Princeton University Press, 1928.

This series of four lectures represents a vigorous, healthy protest against some of the orthodox views on metabolism — always a good sign in science as well as in other fields. Macleod and his school aim particularly to show the possibility of the formation of dextrose from fatty acids, and if they do not prove their point of view conclusively, they display ingenuity in, and diversity of, experimentation and a keenly critical analysis of the work of others as well as their own.

In the first lecture the chemistry of muscular contraction is thoroughly reviewed. The many loopholes possible in the determination of the respiratory quotient are honestly presented so that one feels that the scientific literature would be far better off if all those dealing with respiratory quotients would familiarize themselves with this chapter. One of the important conclusions, based on experiments on depancreatized and hepatectomized animals, is that the respiratory quotient affords no evidence that the tissues of these diabetic animals have any lessened ability to oxidize carbohydrate.

In the second chapter is discussed the manifold relationship between liver glycogen, blood sugar and muscle glycogen. Liver glycogen must be formed to supply the other two products, as shown by experiments on insulin hypoglycemia. An illuminating discussion of the G/N ratio and the demonstration that the hitherto accepted values of 2.8 and 3.65 are too low form an interesting answer to the question of the origin of blood sugar in the absence of liver glycogen; for example, in complete pancreatic diabetes. According to the author, one can account for the high G/N ratio only on the assumption of the formation of considerable dextrose from fatty acid.

The respiratory quotient in muscular exercise, starvation or in one-sided feeding with fat, protein or carbohydrate, and after pancreatomy, forms the material of the third lecture. In spite of the low respiratory quotient in fasting diabetic animals, exercise in the form of shivering can definitely raise it almost as much as in normal animals. In connection with human and phlorizin diabetes, the work of the Lusk school particularly is analyzed, criticized and ultimately lined up in favor of Macleod's theory of the formation of dextrose from fatty acid. Direct proof of the latter seems to be available in the experiments on depancreatized dogs given injections of epinephrine, when much more dextrose was excreted under well controlled conditions than could possibly be accounted for by the prevailing nitrogen metabolism, the breakdown of all the glycogen in the liver and muscles, and the dextrose derivable from glycerol.

The last lecture deals with some of the possible intermediary products of carbohydrate metabolism; such as acetaldehyde, dihydroxyacetone, fructose and methylglyoxal. Of these, the most interesting to clinicians is dihydroxyacetone which has been widely heralded as a substitute for dextrose in the diabetes of human beings. The evidence presented in this chapter clearly dispels any such illusions and shows that, like so many other carbohydrates, dihydroxyacetone is first converted into dextrose and utilized neither more nor less than the latter in animals with diabetes.

This volume has its chief value as a logical critique of much of the prevailing work on carbohydrate metabolism, especially since it comes from the hands of one who is himself one of the masters in that branch of science. It is made attractive reading by its clear style, beautiful type, excellent detailed table of contents and exhaustive modern bibliography, not to speak of the short but com-

plete index. It is to be highly recommended to both clinicians and laboratory men as a source of information and logical reasoning.

THYROXINE. By EDWARD C. KENDALL, M.S., PH.D., D.SC., The Mayo Foundation, Rochester, Minn. Price, $5.50. Pp. 265, with an index and a bibliography of 541 titles. New York: The Chemical Catalog Company, 1929.

This is a useful monograph on the physiology and pathology of the thyroid gland with particular emphasis on the history of the chemical isolation of the active thyroid hormone, thyroxin. The emphasis on the chemical phase comes naturally from the author, Dr. E. C. Kendall, who has done valuable work on the isolation of the hormone. The long list of references will be useful to physicians and investigators who want to go more deeply into the controversial phases of the problem of the thyroid gland than Dr. Kendall has done in the present work. The book is clearly written and is therefore easy reading. Here and there the author goes far afield in speculation, but usually he indicates to the reader that he is on speculative ground. Dr. Kendall states that "thyroxine bridges the gap between living protoplasm and the expression of what may be called personality or temperament. Thyroxine has a definite place in the study of normal and abnormal mental processes." The phenomena usually designated by the terms personality or temperament are not as yet clearly enough defined to be treated profitably in a biochemical monograph. The author further states that "the theoretical deductions in this monograph have been largely based on three contributions: the clinical classification of the goiter and the use of iodine in exophthalmic goiter by Plummer; the isolation of thyroxine; and the extensive studies on basal metabolism in relation to thyroxine and thyroid diseases as carried out by Boothby and his co-workers." In other words, the theoretical deductions reflect largely on the views and practices in the field of study of the thyroid gland represented by the Mayo Clinic. Important as the contributions to physiology, biochemistry, pathology and therapy from the Mayo Clinic are, these by no means constitute the whole story of functions and malfunctions of the thyroid gland as known today. It is useful, however, to have the standpoint of the Mayo Clinic clearly and concisely in one monograph.

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAPH. By HAROLD E. B. PARDEE. Second edition. Price, $5.50. Pp. 242. New York: Paul B. Hoeber, 1928.

This edition of Dr. Pardee's book contains revisions and additions which bring the subject matter up to date. It is written in the same clear style which characterized his first edition and which makes it one of the most readable books on the subject in English. If there is any unfavorable criticism, it lies in the author's tendency to be, perhaps, too dogmatic about some of the alterations in the cardiograph curves under pathologic conditions. These assertions are rare, however, and are perhaps warranted on the basis of clarity for the average user of the book. As the author has intimated, the increasing availability of cardiograph records and knowledge concerning them make just such a book as this worth while for the library of any internist or general practitioner.

WHAT YOU SHOULD KNOW ABOUT HEART DISEASE. By HAROLD E. B. PARDEE. Price, $1.50. Pp. 120. Philadelphia: Lea & Febiger, 1928.

This is a little manual developed along the lines of some of the manuals for diabetic patients except that it is meant for persons interested in heart disease as well as for cardiac patients. As to the advisability of having such a work available there can be little doubt, and this one meets the need so adequately that even though readable by lay persons it could well serve beginning students in medicine for whom it was not primarily intended. Obviously, it should be used in "selected cases" only when the danger of adding a cardiac neurosis to an existing organic circulatory disease is not present. It is a surprisingly complete manual for its size. Many practitioners should welcome it.

BRONCHIAL ASTHMA—ITS DIAGNOSIS AND TREATMENT. By HARRY L. ALEXANDER. Price, $2.25. Pp. 171. Philadelphia: Lea & Febiger, 1928.

The purpose of this book is to present an outline of bronchial asthma. The bibliography correlates the older work with the new, and in this way brings many of the early important studies to the attention of the reader. The factors which underlie an asthmatic paroxysm, the anatomic structures which participate in an attack, the fundamental questions of etiology and the treatment of the disease are well discussed. The chapter on treatment takes up all the modern methods of therapy in a concise manner, and the references are sufficient to allow a detailed study if desired. The book is well written.

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